# Development of Metal-Catalyzed Asymmetric Carbon-Carbon Bond Forming Reactions:

Author: Meredith Suzanne Eno

# The Development of Metal-Catalyzed Asymmetric Carbon-Carbon Bond Forming Reactions

Meredith Suzanne Eno

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**The Development of Metal-Catalyzed Asymmetric Carbon-Carbon Bond Forming Reactions**

Meredith Suzanne Eno

Advisor: James P. Morken, Ph.D.

This dissertation describes the development of four metal-catalyzed carbon-carbon bond forming methods. The first project presented is a palladium-catalyzed proparyl-allyl cross-coupling which proceeds via a kinetic resolution to give enantioenriched 1,5-enynes. Next the asymmetric rhodium-catalyzed hydroformylation of 1-alkenes is described. This reaction delivers synthetically useful a-chiral aldehydes in up to 98:2 er and up to 15:1 branched to linear ratio. The development of a unique nickel-catalyzed asymmetric Kumada coupling of cyclic sulfates is presented. Mechanistic studies reveal the reaction proceeds via an SN2 oxidative addition of a chiral nickel complex. Finally, a-Substituted allyl bis(boronic) esters, which are derived from 1,2-diboration of 1,3-dienes are shown to undergo allylation and subsequent Suzuki coupling with aldehydes tethered to sp2 electrophiles. The carbocycle products obtained bear three contiguous stereocenters and were used as intermediates in the synthesis of complex molecules.

Dedicated to:

My parents, Susan and James Eno

# List of Abbreviations

equiv.: equivalent

eq: equation

SFC: supercritical fluid chromatography

IR: infared spectroscopy

NMR: nuclear magnetic resonance spectroscopy

rt: room temperature

bpy: 2,2'-bipyridine

dme: dimethoxyethane

TBDPS: tert-butyldiphenylsilyl

Nuc: nucleophile

LG: leaving group

$B_2(pin)_2$: bis(pinacolato)diboron

cat: catechol

pin: pinacol

dce: 1,2-dichloroethane

tol: toluene

thf: tetrahydrofuran

dpmu: 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

nmp: N-Methyl-2-pyrrolidone

$PCy_3$: tricyclohexylphosphine

$Pt(dba)_3$: tris(dibenzylideneacetone)platinum(0)

$Pt(dba)_2$: bis(dibenzylideneacetone)platinum(0)

$Pd(PPh_3)_4$: tetrakis(triphenylphosphine)palladium(0)

D-*t*-BPF: 1,1'-bis(di-*tert*-butylphosphino)ferrocene

MeCN: acetonitrile

dppp: 1,3-bis(diphenylphosphino)propane

dppf: 1,1'-ferrocenediyl-bis(diphenylphosphine)

tBuXPhos: 2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl

CsF: cesium fluoride

NBS: N-bromosuccinimide

DIBAL-H: diisobutylaluminum hydride

MNBA: 2-methyl-6-nitrobenzoic anhydride

DMAP: 4-dimethylaminopyridine

BPE: bisphospholanoethane

$Rh(acac)(CO)_2$: (acetylacetonato)dicarbonylrhodium(I)

$[RhCl(C_2H_4)_2]_2$: chlorobis(ethylene)rhodium(I) dimer

$[Rh(NBD)Cl]_2$: bicycle[2.2.1]hepta-2,5-dienerhodium(I) chloride dimer

$[Rh(OMe)COD]_2$: methoxy(cyclooctadiene)rhodium(I) dimer

PMB: *p*-methoxybenzyl

Bz: benzoyl

TFA: trifluoroacetate

MFB: Bis(di-2-furanylphosphino)-6,6'dimethoxy-1,1'-biphenyl

DACC: Diboration Allylation Cross-Coupling

AHF: Asymmetric Hydroformylation

DFT: density functional theory

Ac: acetate

THP: tetrahydropyran

PyBox: pyridine bis(oxazoline)

Box: bis(oxazoline)

Phox: phosphinooxazolines

DAST: diethylaminosulfur trifluoride

$Im_2SO_2$: 1,1'-sulfonyldiimidazole

MK-10: montmorillonite K10

dma: dimethylacetamide

TMEDA: tetramethylethylenediamine

9-BBN: 9-borabicyclo(3.3.1.)nonae

DTBMP: 2,6-di-*t*-butyl-4-methylpyridine

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# Chapter 1

# Accessing Enantioenriched 1,5-Enynes through Palladium Catalyzed Resolution of Racemic Propargyl Electrophiles *via* Allyl-Propargyl Cross-Coupling

## 1.1 Introduction

1,5-Dnynes are useful synthetic intermediates that offer differentiated $\pi$-systems, which can be functionalized selectively to build complexity in natural product syntheses. Recently, we have demonstrated that optically enriched 1,5-enynes can be accessed through a stereospecific Pd-catalyzed allyl-propargyl cross coupling reaction with high regioselectivity, yield and near-perfect conservation of enantiopurity.[1] Accessing the optically enriched propargyl acetates can often take several steps. Herein the efforts to develop a method to access optically active 1,5-enynes through the resolution of readily available racemic propargyl electrophiles will be described.

## 1.2 Background Allylboronate Synthesis and Utility

In this chapter, I will present a palladium-catalyzed allyl-propargyl cross-coupling that converts allyl boronates to 1,5-enynes. In the following background chapter, I will describe the synthetic utility of these reaction products and previous methods for their synthesis.

[1] Ardolino, M.J; Morken, J.P. *J. Am. Chem. Soc.* **2012**, *134*, 8770.

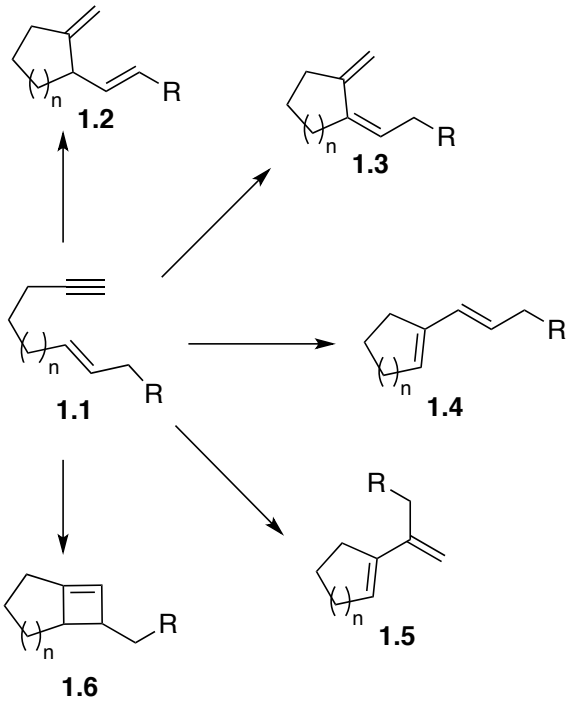
### *1.2.1 Synthetic Utility of 1,5-Enynes*

Metal-catalyzed cycloisomerizations of acyclic enynes has become a useful method to quickly build up complexity in natural product syntheses due the reactions high atom economy.[2] Since the discovery of the catalytic Alder-ene reaction in 1984 (**1.1** -> **1.2**), several different metal catalyzed cycloisomerizations have been discovered (Scheme 1.1).[3] A majority of these strategies are limited to the reaction of 1,7- and 1,6-enynes. 1,5-Enyne systems are less studied and stereogenicity on the intervening methylenes in the chain is usually lost during the course of the reaction. There are a few examples of cyclizations of 1,5-enynes that proceed stereospecifically if enantioenriched 1,5-enynes are employed.

[2] For Reviews on 1,n-enyne cycloisomerizations see: a) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268. b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. c) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

[3] (a) Trost, B. M.; Lautens, M.; Hung, H., Carmichael, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 7641. (b) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651. (c) Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268.

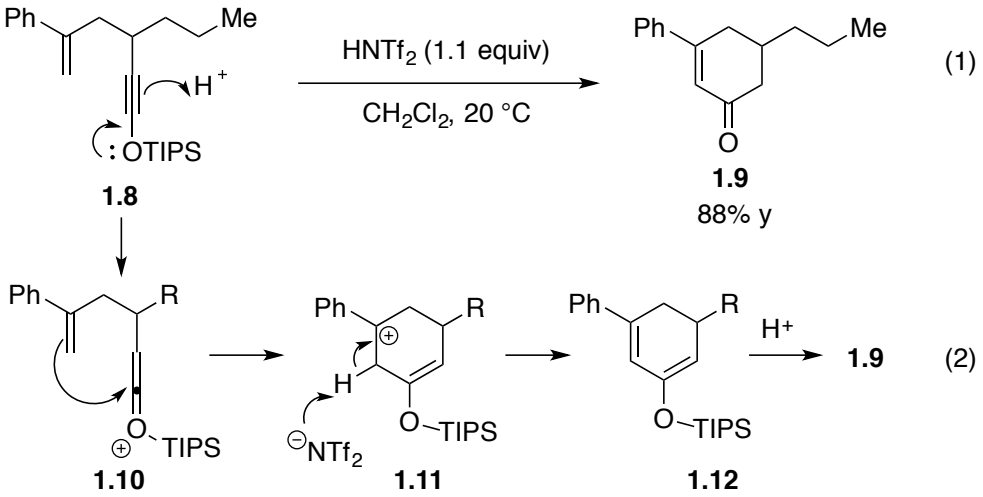
**Scheme 1.1: Cycloisomerizations of Enynes**




In 2004, Kozmin and Zhang reported the first Brønsted acid-mediated cyclization of siloxyalkynes to form substituted cyclohexanones (Scheme 1.2).[4] Upon protonation of the siloxy alkyne **1.8** with bis(trifluoromethane)sulfonimide, a highly reactive ketenium ion, **1.10** is formed. Nucleophilic attack of the alkene followed by deprotonation yields the conjugated silyl enol ether **1.12.** The final cyclohexenone **1.9** is formed after acid work-up. The authors note that stoichiometric amounts of the Brønsted acid are required for efficient cyclization.

[4] Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204.

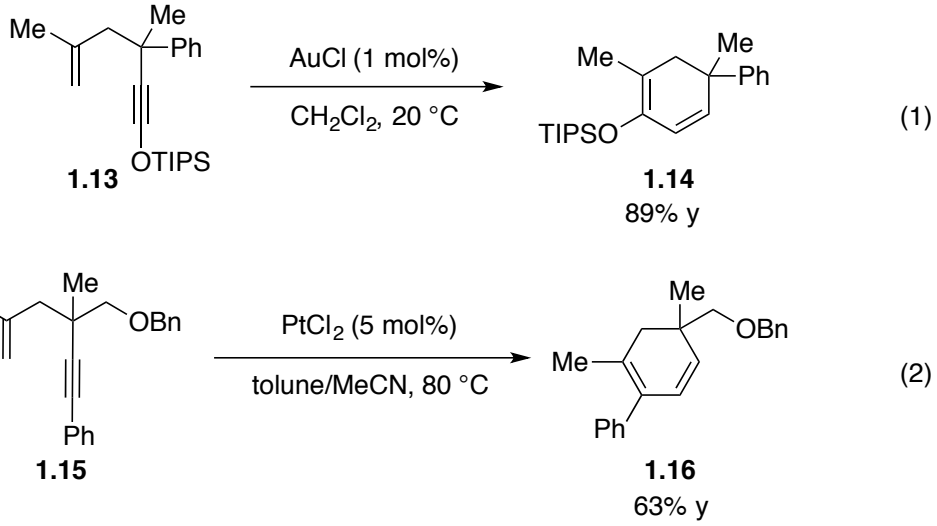
**Scheme 1.2: Synthesis of Cyclohexanones by Acid-Promoted Cyclization**




Two years later, while searching for a catalytic strategy to achieve the above transformation, the group discovered a novel cycloisomerization using gold catalysts (Scheme 1.3, eq. 1).[5] With catalytic amounts of AuCl, siloxy eynes **1.13** are smoothly converted into substituted cyclohexadienes **1.14**. After some mechanistic investigation, it was determined that the reaction proceeds through a series of unique 1,2-alkyl shifts. Later, the Kozmin group found that a platinum catalyst was required to perform the cycloisomerization on aryl alkynes **1.15.** It is also noteworthy that the cycloisomerization proceeds without racemization of pendant stereocenters, allowing access to highly functionalized enantioenriched cyclohexadienes from optically pure 1,5-enynes (Scheme 1.3, eq. 2).

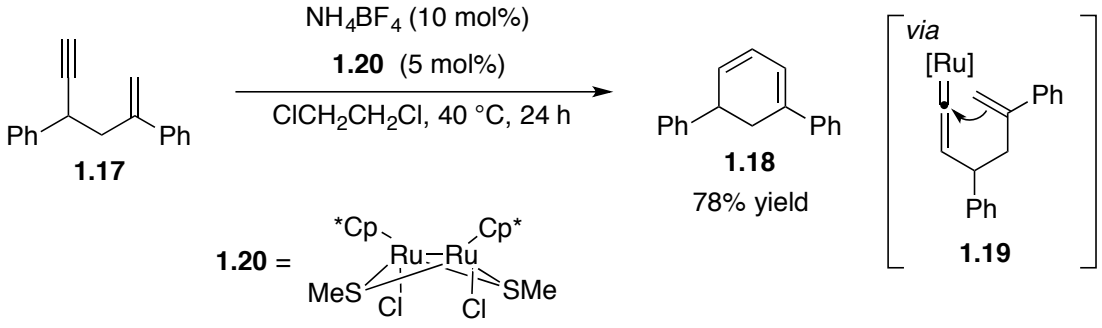
[5] Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705.

**Scheme 1.3: Synthesis of Substituted Cylohexadienes via Cycloisomerization of Enynes**




In 2009, Nishibayashi and co-workers utilized methanethiolate bridged diruthenium complex **1.20** to achieve a similar transformation of 1,5-enynes to cyclohexadienes (Scheme 1.4).[6] This reaction is proposed to proceed via nucleophilic attack of the alkene on the Ru-vinylidene intermediate **1.19**, followed by proton transfer.

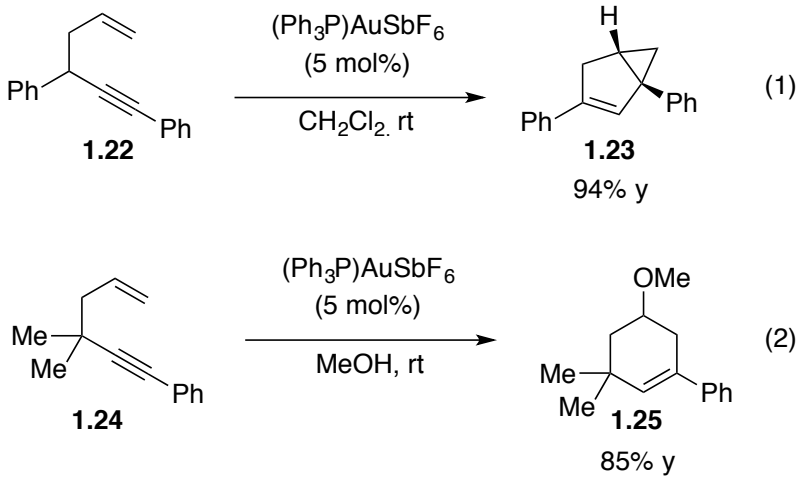
**Scheme 1.4: Nishibayahi's Ru-Catalyzed Cycloisomerization of 1,5-Enynes**




[6] Fukamizu, K.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 2534.

In addition to the formation of cyclohexadienes from 1,5-enynes, Toste and co-workers have developed a gold(I)-catalyzed cycloisomerization to access bicyclo[3.1.0]hexanes **1.23** (Scheme 1.5, eq. 1).[7] During their mechanistic studies, in an attempt to trap intermediate carbocations, the authors discovered that if the reaction is carried out in methanol, clean formation of cyclohexenyl methyl ether **1.25** is observed (Scheme 1.5, eq. 2). This nucleophile trapping strategy allows access to an entirely different and interesting scaffold from the desired bicyclo[3.1.0]cyclohexanes obtained.

**Scheme 1.5: Gold-Catalyzed Cyclization of 1,5-Enynes by Toste**

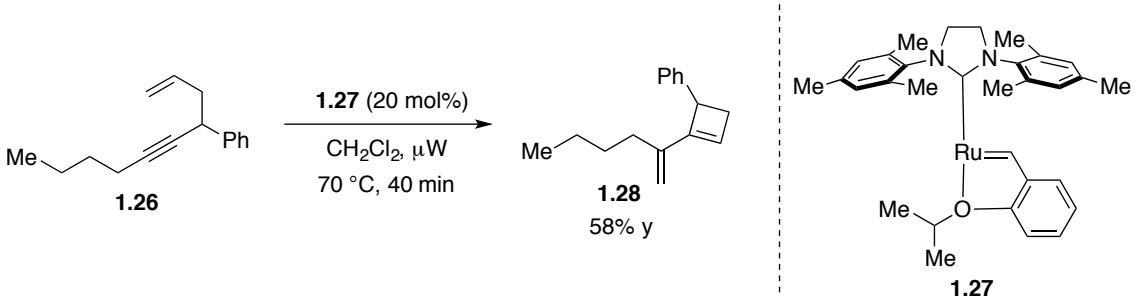



In 2007, a HG-II (**1.27**) catalyzed enyne-ring closing metathesis of 1,5-enynes was presented by Campagne and co-workers (Scheme 1.6).[8] Under microwave irradiation at 70 °C with HG-II 1,5-enyne **1.26** is transformed into the corresponding cyclobutene **1.28** in moderate yield. Ring closing metathesis was previously believed to be non-ideal for the

[7] Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858.
[8] Debledes, O.; Campagne, J.-M. *J. Am. Chem. Soc.* **2008**, *130*, 1562.

synthesis of strained cyclobutenes due to reopening by the carbene catalyst. The authors propose that this transformation is possible because cyclobutenes **1.28** may be less prone to ring opening by the catalyst due preferential coordination of the catalyst to the less hindered terminal olefin.

**Scheme 1.6: Ring-Closing Metathesis of 1,5-Enynes**




*1.2.2 Synthesis of 1,5-Enynes*

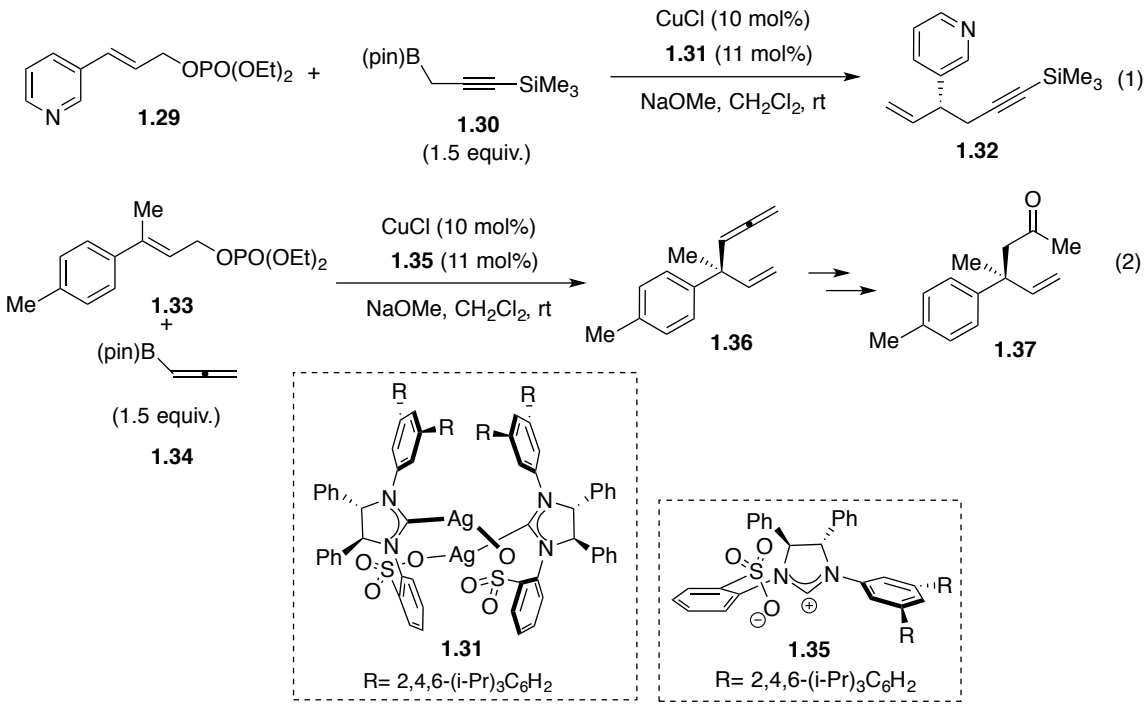
Due to the diversity of products one can obtain from 1,5-enynes, catalytic enantioselective methods to synthesize these scaffolds are important. At the beginning of our efforts towards developing a facile route to enantioenriched 1,5-enynes, there were no general ways to synthesize these scaffolds with high optical purity. However, in 2015 after our studies, in efforts to further expand the scope of copper-catalyzed enantioselective allylic substitution, Hoveyda and co-workers presented an efficient,

selective route to enantioenriched 1,5-enynes with allylic stereocenters.[9] Utilizing an *in situ* generated chiral copper-NHC complex (CuCl + **1.31**), addition of trimethylsilylsubstituted propargylboron **1.30** to allylic phosphates proceeds with high regio- and enantioselectivies (Scheme 1.7, eq. 1). Previously, Hoveyda and co-workers had developed a related enantioselective addition of allenylB(pin) **1.34** to allylic phosphates to form allenyl containing products **1.36** (Scheme 1.7, eq.2).[10] Additionally, they demonstrated the utility of such systems through the hydroboration and oxidation of the allene to yield useful β-vinyl ketones **1.37**.

[9] Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948. For previous examples of enantioselective allylic substitution with allylic phosphates see: (a) Gao, F.; Carr, L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 2149. (b) Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778. (c) Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 8370. (d) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006,** *128*, 15604. (e) Kacprzynski, M. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 10676.

[10] Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490.

**Scheme 1.7: Enantioselective Allylic Substitution by Hoveyda**

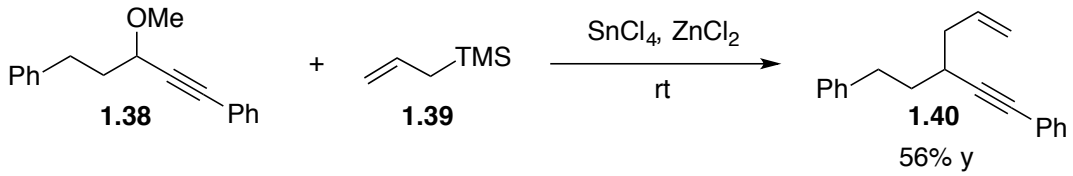



Though the use of enantioselective allylic substitution has not seen much use in the synthesis of 1,5-enynes, applications of this strategy to form 1,4-enynes is known with copper and iridium catalysts.[11] Besides allylic substitution, the majority of the methods to access 1,5-enynes involve Lewis acid assisted allylation of propargyl electrophiles. The first example of this strategy was presented by Hayashi and co-workers in 1987.[12] Allylation of propargylic ether **1.38** with allyl trimethylsilane **1.39** in the presence of catalytic amounts of $SnCl_4$ and $ZnCl_2$ produces 1,5-enyne **1.40** in 56% yield (Scheme 1.8).

[11] (a) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7532. (b) Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778

[12] Hayashi, M.; Inubushi, A.; Mukaiyama, T. *Chem. Lett.* **1987**, 1975.

**Scheme 1.8: Seminal Example of Lewis Acid Mediated Allylic Substitution to access 1,5-Enynes**

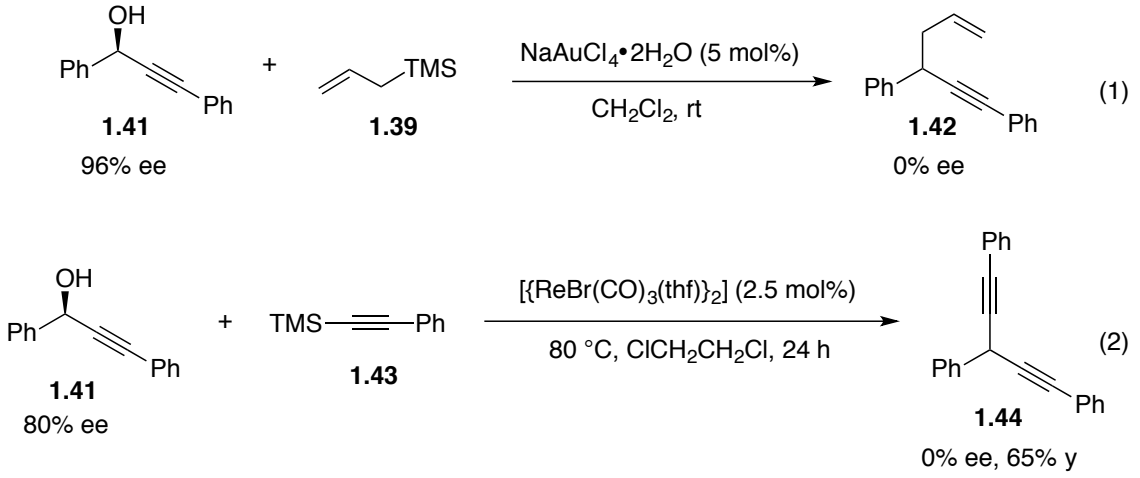



Since this report, several other transition metal-based Lewis acids such as complexes of Re, Zn, Fe, and Cu have been shown to catalyze the reaction of allylsilanes with propargyl alcohols to yield 1,5-enynes.[13] Mechanistically, these reactions are proposed to proceed via stabilized carbocations. In 2005, Campagne and co-workers demonstrated the loss of optical purity in their gold catalyzed allylation of propargyl alcohols, supporting the intermediacy of an achiral carbocation (Scheme 1.9, eq. 1).[14] Takai and co-workers have also demonstrated this phenomenon; in their rhenium catalyzed allylation or alkynlation of propargyl alcohols (Scheme 1.9, eq. 2). Reaction of enantioenriched propargyl alcohol **1.41** with trimethyl(phenethynyl)silane **1.43** in the presence of rhenium catalyst resulted in racemic diyne **1.44** supporting the formation of a propargyl carbocation under the reaction conditions (Scheme 1.9, eq. 2).

[13] a) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180. (b) Yadav, J. S.; Reddy, B. V. S.; Rao, T. S.; Rao, K. V. R. *Tetrahedron Lett.* **2008**, *49,* 614. (c) Kuninobu, Y.; Ishii, E.; Takai, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 3296. (d) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760. (e) Zhan, Z.-p.; Yu, J.-l.; Liu, H.-j.; Cui, Y.-y.; Yang, R.-f.; Yang, W.-z.; Li, J.-p. *J. Org. Chem.* **2006**, *71*, 8298.

[14] Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180.

**Scheme 1.9: Racemization During Allylic Substitution of Propargyl Electrophiles**



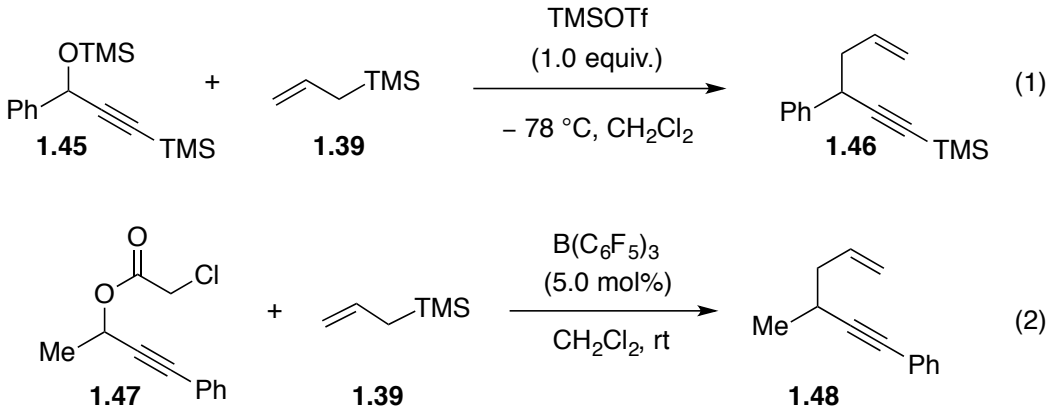

Organic Lewis acids have also been utilized in substitution reactions of propargyl electrophiles.[15] In 2001, Ishikawa and Saito showed that propargyl silyl ethers could be activated with stoichiometric amounts of TMSOTf and reacted with a variety of nucleophiles, including allylsilanes (Scheme 1.10, eq 1).[16] Gevorgyan and co-workers have shown $B(C_6F_5)_3$ as an excellent catalyst for the allylation of propargyl acetates **1.47** with allyl silane **1.39**.[17] This is an attractive method since only catalytic amounts of the Lewis acid are needed and the scope is broad compared to catalytic propargylic substitutions with transition-metal based Lewis acids.

[15] (a) Weng, S. S.; Hsieh, K.-Y.; Zheng, Z.-J. *Tetrahedron*, **2015**, *71*, 2549. (b) Nitsch, D.; Huber S. M.; Poethig, A.; Narayanan, A.; Olah, G. A.; Prakash, G. K.; Bach, T. *J. Am. Chem. Soc.* **2014**, 136, 2851. (c) Kabalka, G. W.; Yao, M.-L.; Borella, S. *J. Am. Chem. Soc.* **2006**, *128*, 11320. (d) Sanz, R.; Martínez, A.; Álvarez- Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2006**, 1383.

[16] Ishikawa, T.; Okano, M.; Aikawa, T.; Saito, S. *J. Org. Chem.* **2001**, *66*, 4635.

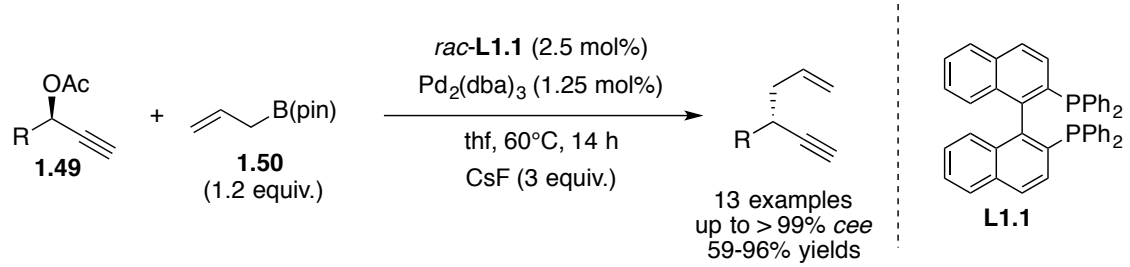
[17] Schwier, T.; Rubin, M.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1999.

**Scheme 1.10: Organic Lewis Acids Mediated Allylic Substitution of Propargyl Electrophiles**




The synthesis of 1,5-enynes through nucleophilic propargylic substitution with allyl nucleophiles in the presence of catalytic or stoichiometric Lewis acids is a simple high yielding route to the desired 1,5-enynes. However, due to the intermediacy of carbocation species during the mechanism, an enantioselective propargylic substitution has not been developed. Our group has recently demonstrated that enantioenriched 1,5-enynes can be accessed through a stereospecific palladium-catalyzed propargyl-allyl cross-coupling (Scheme 1.11).[18]

**Scheme 1.11: Stereospecific Propargyl-Allyl Cross-Coupling**




[18] Ardolino, M.J; Morken, J.P. *J. Am. Chem. Soc.* **2012**, *134*, 8770.

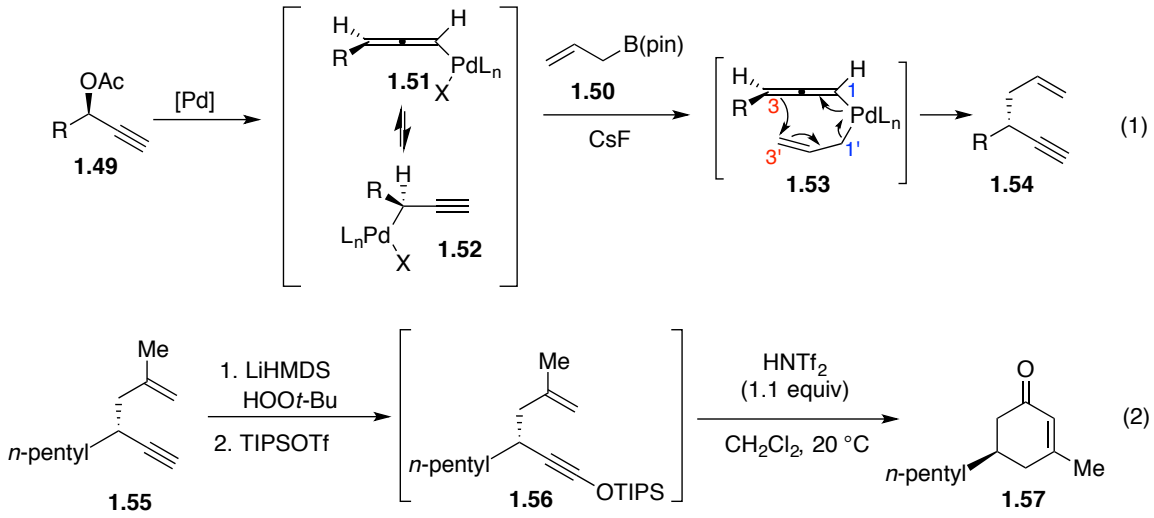
This reaction proceeds by palladium undergoing a stereospecific $S_N2'$ oxidative addition with enantioenriched propargyl electrophiles **1.49** to give configurationally stable $\eta^1$-(allenyl)palladium intermediate **1.51**, which can isomerize to $\eta^1$-(propargyl)palladium **1.52** (Scheme 1.12, eq. 1)).[19] After transmetalation of allyl B(pin) **1.50** a 3,3' reductive elimination from **1.53** furnishes the desired 1,5-enyne with high regioselectivity, yield and near-perfect conservation of enantiopurity.[20] $\eta^1$-(Allenyl)palladium intermediate **1.51** is more stable than **1.52**, due to increased steric interactions between the palladium and R group on the electrophile in **1.52**. Also, because the carbon-palladium bond at the $sp^2$ hybridized bond is stronger. The utility of this method was demonstrated by synthesizing enantioenriched cyclohexanone **1.57** from 1,5-enyne **1.55** using conditions developed by Kozmin and co-workers (Scheme 1.12, eq. 2).[4] This work marked the first method developed to access 1,5-enynes in high optical purity. However, obtaining the enantioenriched propargyl alcohols is not always straight forward. For this reason, we were interested in developing a method to access optically enriched 1,5-enynes from readily available racemic propargyl electrophiles.

---

[19] (a) Elsevier, C. J. Kleijn, H.; Boersma, J.; Vermeer, P. *Organometallics* **1986**, *5*, 716. (b) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687. (c) Baize, M. W.; Blosser, P. W.; Plantevin, V.; Schimpff, D. G.; Gallucci, J. C.; Wojcicki, A. *Organometallics* **1996**, *15*, 164.

[20] For previous example of 3,3'-reductive eliminations in palladium catalyzed cross-coupling see: (a) Ardolino, M. J.; Morken, J. P. *Tetrahedron* **2015**, *71*, 6409. Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 10686. (b) Zhang, P.; Le, Hai.; Kyne, R. E.; Morken, *J. P. J. Am. Chem. Soc*. **2011**, *133*, 9716. (c) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778.

**Scheme 1.12: Stereospecific Pd-Catlayzed Propargyl-Allyl Cross-Coupling and Synthetic Utility**



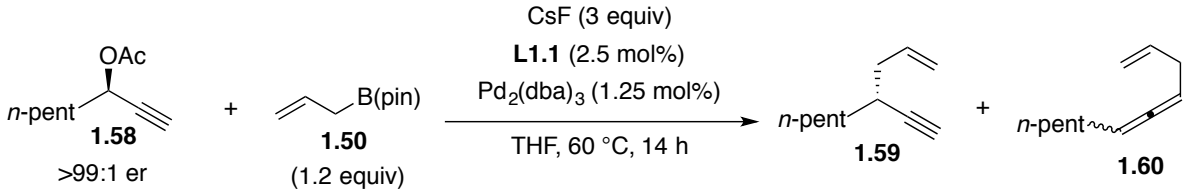

## 1.3 Development of a Kinetic Resolution of Propargyl Electrophiles to Access Enantioenriched 1,5-Enynes[21]

### *1.3.1. Initial Results for Kinetic Resolution and Optimization*

During the development of the stereospecific propargyl-allyl cross-coupling described above, a slight matched/mismatched character with opposite enantiomers of ligand was observed (Table 1.1)

[21] Ardolino, M. J.; Eno, M. S.; Morken, J. P. *Adv. Synth. Catal.* **2013**, *17*, 3413.

**Table 1.1: Matched/Mismatched Catalyst Substrate Interactions in Stereospecific Cross-Coupling**



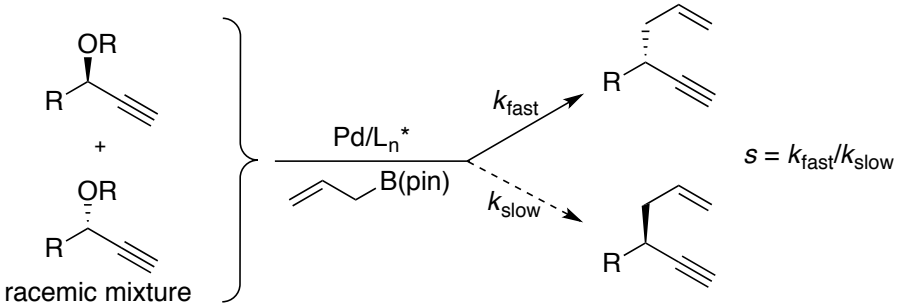

| entry | ligand | **1.59:1.60** | er **1.59** |
|---|---|---|---|
| 1 | *rac* | 98:2 | >99:1 |
| 2 | *(R)* | 99:1 | >99:1 |
| 3 | *(S)* | 93:7 | 98:2 |

We began to consider that rather than performing a stereospecific cross-coupling we could further optimize these conditions to allow for a kinetic resolution.[22] Advantageously, this strategy can allow access to enantioenriched 1,5-enynes from readily available racemic propargyl electrophiles (Scheme 1.13). Though there are a few examples of kinetic resolutions of allylic electrophiles, a kinetic resolution with propargyl electrophiles has yet to be developed.[23]

[22] For reviews on kinetic resolutions see: (a) Vedejas, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974. (b) Kagan, H.B.; Fiaud, J.C. *Topics in Stereochem.* **1988**, *18*, 249-330. (c) Keith, J.M.; Larrow, J.F.; Jacobsen, E.N. *Adv. Syn. Cat.* **2001**, *343*, 5. (d) Cook, Gregory R. *Current Organic Chemistry*, **2000**, *4*, 869.

[23] (a) Choi, Y. K.; Suh, J. H.; Lee, D.; Lim, I. T.; Jung, J. Y.; Kim, M. J. *J. Org. Chem.* **1999**, *64*, 8423. (b) Gais, H. J.; Bondarev, O.; Hetzer, R. *Tetrahedron Lett.* **2005**, *46*, 6279. (c) Mao, B.; Ji, Y.; Fañanás-Mastral, M.; Caroli, G.; Meetsma, A.; Feringa, B. *Angew. Chem. Int. Ed.* **2012**, *51*, 3168.

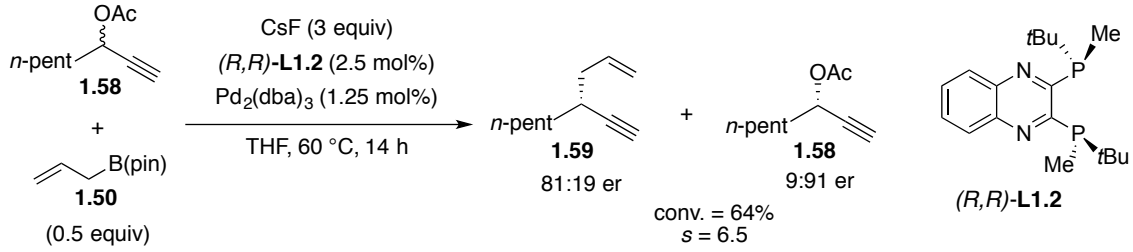
**Scheme 1.13: Proposed Kinetic Resolution of Propargyl Electrophiles to Access Enantioenriched 1,5-Enynes.**




The development of the kinetic resolution of propargyl acetates was initiated by treating propargyl acetate **1.58** with 0.5 equivalents of allylB(pin) **1.50** under the previously optimized conditions for the stereospecific propargyl-allyl cross-coupling with **L1.2**. We were pleased to see that the reaction gave a moderate resolution to the desired 1,5-enyne **1.59**, which was isolated in 81:19 er, and the recovered the acetate in was obtained 9:91 er. With 64% conversion of starting material, a selectivity factor of 6.5 was calculated.[24] We needed to further enhance the resolving power of the reaction and predicted that the ligand scaffold would have a significant impact on the reaction.

[24] $s = \ln[(1-C/100)(1-ee_{\mathbf{1.58}}/100)]/\ln[(1-C/100)(1+ee_{\mathbf{1.59}}/100)]$. $C = ee_{\mathbf{1.58}}/(ee_{1.58}+ee_{\mathbf{1.59}})$

**Scheme 1.14: Initial Results of Kinetic Resolution**



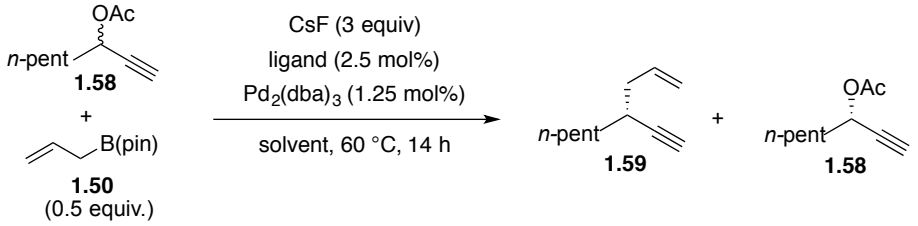

We surveyed the utility of a variety of bidentate phosphine ligand scaffolds in the reaction with propargyl acetate **1.58** (Table 1.2). Previous studies have shown that bidentate phosphine ligands with smaller biaryl dihedral angles show protrusion of the equatorial aromatic rings of the phosphines in crystal structures.[25] Similarly, biaryl dihedral angle have been correlated to the enantiosectivity of a variety of reactions, with smaller dihedral angles leading to more enantioselective reactions in some cases.[26] We found a similar trend with selectivity factors increasing with decreasing dihedral angles. Segphos **L1.4** has the smallest dihedral angle at 65.0° and gives the highest *s* factors out of the phenyl substituted bidentate phosphines **L1.5** (68.6°) and **L1.1** (74.4°) (entries 3, 2). We considered that perhaps oxidative addition or alkyne binding is the selectivity determining step and that slow oxidative addition would lead to a more efficient resolution. Since oxidative addition is generally favored with electron-rich metal centers

[25] (a) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405. (b) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

[26] (a) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, 1931. (b) Zhang, X.; Raghunath, M. *Tetrahedron Lett.* **2005**, *46*, 8213.

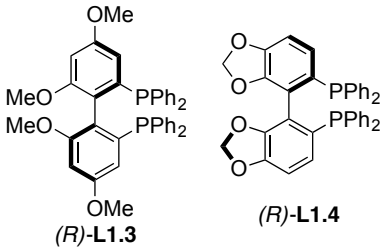
we predicted that electron poor donor ligands could slow oxidative addition.[27] We were pleased to observe that changing to electron withdrawing groups on the phosphine, such as furyl rings in **L1.6**, led to significantly higher resolving power in the reaction ( *s* = 18.6, entry 7).

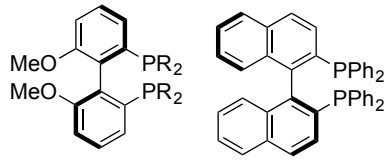
**Table 1.2: Ligand Optimization in Kinetic Resolution**




| entry | ligand | dihedral angle | er **1.59** | er **1.58** | conv. (%) | *s* |
|---|---|---|---|---|---|---|
| 1 | (*R*)-**L1.2** | | 85:15 | 37:63 | 27 | 7.3 |
| 2 | (*S*)-**L1.1** | 74.4° | 29:71 | 73:27 | 52 | 3.8 |
| 3 | (*R*)-**L1.5** | 68.6° | 77:23 | 16:84 | 56 | 6.6 |
| 4 | (*R*)-**L1.3** | | 70:30 | 17:83 | 63 | 4.2 |
| 5 | (*R*)-**L1.4** | 65.0° | 82:12 | 23:77 | 46 | 7.7 |
| 6 | (*R*)-**L1.7** | | 60:40 | 39:61 | 52 | 1.9 |
| 7 | (*R*)-**L1.6** | | 89:11 | 11:89 | 50 | 18.6 |

[a]Conversion calculated by the following equation; $C = ee_{SM}/(ee_{SM} + ee_{PR})$. Enantiomeric excesss determined by GC analysis on a chiral stationary phase.




*(R)*-**L1.5** R= Ph
*(R)*-**L1.6** R= furyl

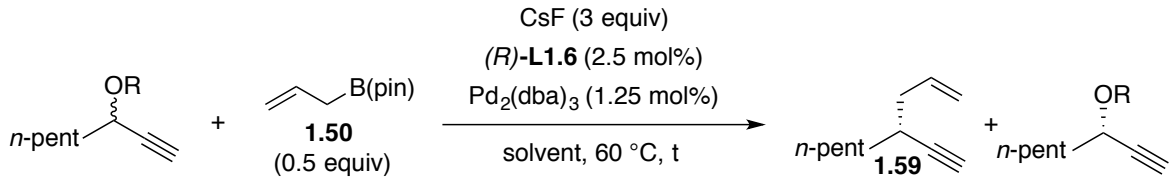
*(R)*-**L1.1** R= Ph
*(R)*-**L1.7** R= xylyl

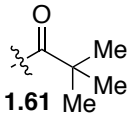
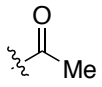
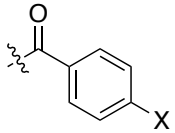
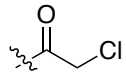
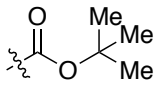
We also predicted that the leaving group ability of the electrophile would influence the rate of oxidative addition, and if that is in fact the stereochemistry determining step, manipulating this could increase the effectiveness of the resolution

[27] Hartwig, J. F.; *Organotransistion Metal Chemistry*; University Science Books: Mill Valley, Ca, 2010, 261-317.

(Table 1.3). Unfortunately, worse leaving groups, such as the unprotected alcohol or silyl protected alcohols led to no reaction under the optimized conditions. We were able to observe a trend with benzoate protecting groups: with electron donating groups **1.63** gave slightly higher s factors than those with electron withdrawing groups **1.64**, indicating that the leaving group ability does influence the efficiency of the resolution.

**Table 1.3: Optimization of Electrophile in Kinetic Resolution**

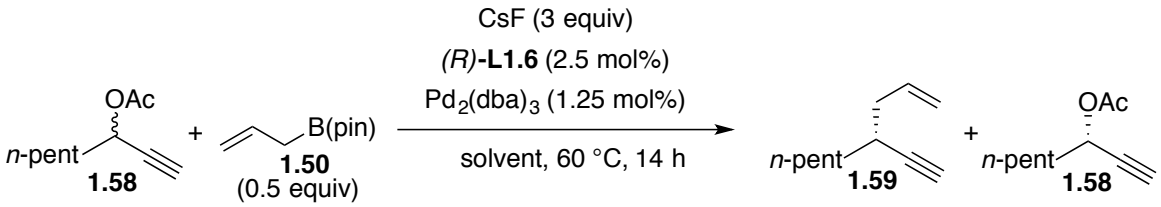



| R | x | entry | t (hr) | er $_{PR}$ | er $_{SM}$ | conv. (%) | *s* |
|---|---|---|---|---|---|---|---|
|  **1.61** | | 1 | 14 | 84:16 | 97:3 | 58 | 17.9 |
|  **1.58** | | 2 | 14 | 89:11 | 11:89 | 50 | 18.6 |
|  | **1.62** x=H | 3 | 5 | 92:8 | 59:41 | 18 | 12.5 |
| | **1.63** x= $OCH_3$ | 4 | 5 | 81:19 | 98:2 | 61 | 15.0 |
| | **1.64** x= Br | 5 | 5 | 92:8 | 44:56 | 14 | 12.3 |
|  **1.65** | | 6 | 2 | 74:26 | 1:99 | 67 | 10.5 |
|  **1.66** | | 7[b] | 5 | 89:11 | n.d. | 19 | 2.7 |

[a]Conversion calculated by the following equation; C = $ee_{SM}/(ee_{SM} + ee_{PR})$. Enantiomeric excesss determined by GC analysis on a chiral stationary phase. [b]Conversion calculated based on starting material using 1H-NMR.

Our final optimization efforts were focused on changing reaction conditions to increase the selectivity factors (Table 1.4). It seemed that the nature of the solvent did not lead to drastic changes in selectivity except for in coordinating solvents such as DMF (entry 6). The temperature of the reaction had little effect on the s factor of the reaction with 25, 40 and 60 °C leading to similar s factors. After optimization, we determined that running the reaction at 60 °C in tetrahydrofuran with **L1.6** would be our ideal conditions to investigate other electrophiles in the resolution.

**Table 1.4: Optimization of Reaction Conditions for Kinetic Resolution**

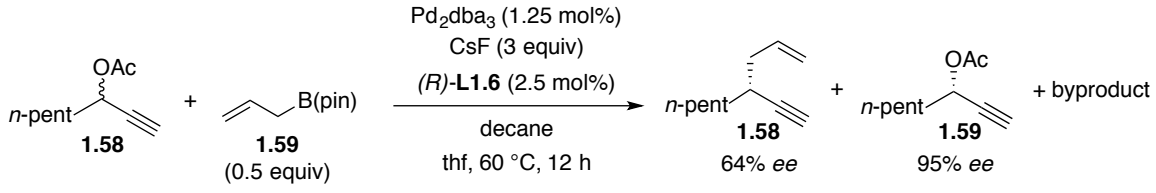



| entry | solvent | er **1.59** | er **1.58** | conv. (%) | $s^c$ |
|---|---|---|---|---|---|
| 1 | THF | 89:11 | 11:89 | 50 | 18.6 |
| 2 | Me-THF | 88:12 | 11:89 | 51 | 17.1 |
| 3 | TBME | 92:8 | 39:61 | 20 | 14.0 |
| 4 | $CH_3CN$ | 90:10 | 40:60 | 20 | 11.3 |
| 5 | $CH_2Cl_2$ | 84:16 | 15:85 | 51 | 10.8 |
| 6 | DMF | 66:34 | 20:80 | 65 | 3.4 |

[a]Conversion calculated by the following equation; $C = ee_{\mathbf{1.58}}/(ee_{\mathbf{1.58}} + ee_{\mathbf{1.59}})$. Enantiomeric excesss determined by GC analysis on a chiral stationary phase.

It is important to note that throughout the optimization of the kinetic resolution the conversions were calculated based on the enantioselectivities of the product and starting material obtained using an equation developed by Kagan.[28] However, this method relies on the assumption that the starting material is converted to the product with no side reactions. With our optimized conditions in hand, we wanted to ensure that this method was accurate in determining the conversion of the reaction. Comparing the conversion of **1.59** in the resolution using the equation developed by Kagan, using $^{1}$H-NMR analysis, or by GC analysis showed a slight variation in conversion (Scheme 1.15). Using a more accurate method to determine conversion, GC with an internal standard, indicated a higher conversion than was determined than with the Kagan equation. Throughout our investigation, our method to determine conversion led to artificially high selectivity factors. During this investigation, a previously undetected unidentified byproduct was observed.

**Scheme 1.15: Comparison of Methods to Determine Conversion with $Pd_2(dba)_3$**



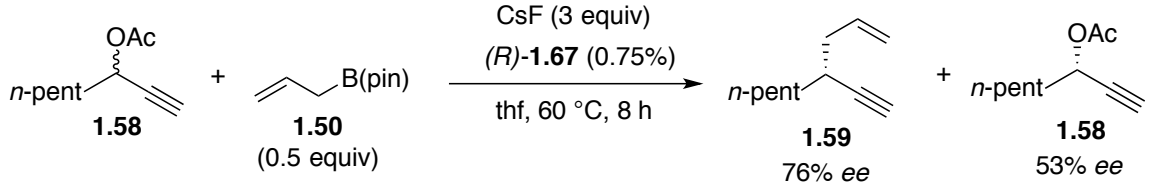

| method | conv. (%) | *s* |
|---|---|---|
| calculated | 59.8 | 15.7 |
| $^{1}$H-NMR | 64.9 | 10.6 |
| GC | 62.6 | 12.2 |

[28] Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry.* **1988**, *18*, 249-330.

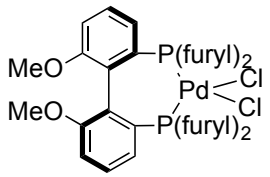
Efforts were next expanded to find a more reliable catalyst system that could potentially lead to reproducible and accurate selectivity factors without byproduct formation. $Pd_2dba_3$ is a common palladium(0) pre-catalyst, however; it has been documented that commercial sources contain small amounts of active catalyst, free dibenzylidenediacetone (dba), and palladium nanoparticles.[29] It is known that also known that dba from the palladium can inhibit reactions and the nanoparticles could lead to undesired reactivity.[30] We predicted that a different palladium pre-catalyst could lead to a cleaner reaction and a preformed $PdCl_2$/MFB complex **1.67** was prepared to test this hypothesis. Gratifyingly, complex **1.67** lead to a cleaner reaction and more accurate calculated selectivity factors (Scheme 1.16). The preformed catalyst also allowed for a drop in catalyst loading to 0.75 mol% while still maintaining resolving power and efficiency.

[29] Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302.
[30] Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178-180*, 511. b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F.; McGlacken, G. P.; Weissburger, F.; de Vries, A. H. M.; Schmieder-van de Vondervoort, L. S. *Chem. –Eur. J.* **2006**, *12*, 8750. c) Fairlamb, I. J. S. *Org. Biomol. Chem.* **2008**, *6*, 3645.

**Scheme 1.16: Comparison of Methods to Determine Conversion with 1.67 Precatalyst**




| method | conv. (%) | *s* |
|---|---|---|
| calculated | 41.3 | 12.1 |
| $^1$H-NMR | 41.8 | 11.3 |



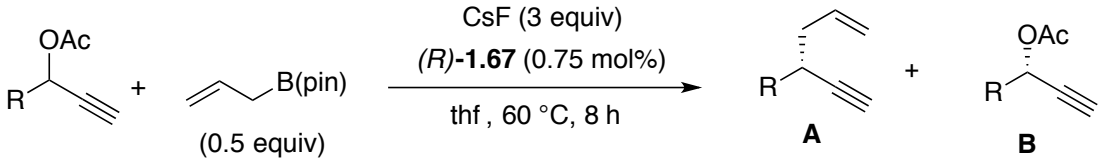

**1.67**

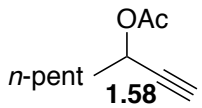
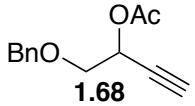
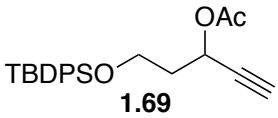
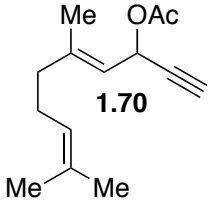
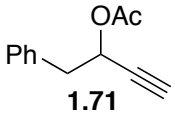
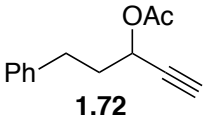
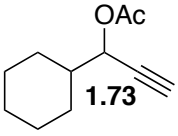
*1.3.2. Scope of Kinetic Resolution of Propargyl Acetates*

Having determined conditions to give a highly efficient and selective kinetic resolution, we began to investigate other propargyl acetates (Table 1.5). In addition to aliphatic propargyl acetate **1.58**, electrophiles with a pendant benzyl protected alcohol gave similar selectivites, while a bulky TBDPS protected alcohol gave a large increase in selectivity factor to 26.3 (entry 2, 3). Substituents containing unsaturation on the chain were tolerated in the reaction, though with decreased selectivity factors (entry 4, 5, 6).

Increasing the steric bulk on the chain with a cyclohexyl group lead to a much slower reaction with no improvement in selectivity (entry 7).

**Table 1.5: Kinetic Resolution of Aliphatic Propargyl Acetates**

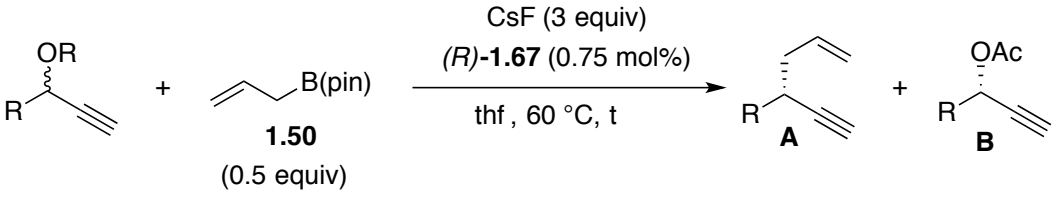


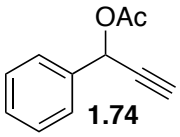
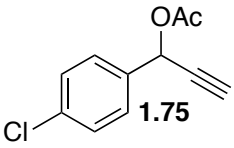
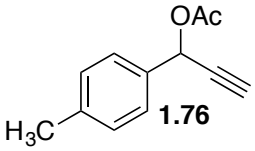
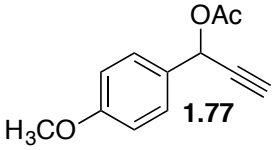
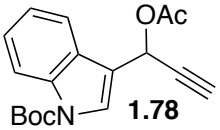
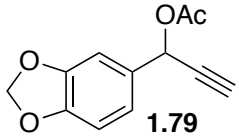

| entry | substrate | run no. | t (h) | er **A**[a] | er **B**[a] | conv(%)[b] | $s_{AVG}$[d] |
|---|---|---|---|---|---|---|---|
| 1 |  **1.58** | 1 | 8 | 88:12 | 85:15 | 48 | 14.5 |
| | | 2 | 8 | 86:14 | 87:13 | 50 | |
| 2 |  **1.68** | 1 | 8 | 87:13 | 72:28 | 37 | 11.1 |
| | | 2 | 8 | 88:12 | 74:26 | 39 | |
| 3[b] |  **1.69** | 1 | 12 | n.d. | 74:26 | 36 | 26.3 |
| | | 2 | 12 | n.d. | 75:25 | 36 | |
| 4 |  **1.70** | 1 | 12 | 87:13 | 70:30 | 42 | 26.3 |
| | | 2 | 12 | 82:18 | 77:23 | 46 | |
| 5 |  **1.71** | 1 | 4 | 85:15 | 61:39 | 24 | 6.5 |
| | | 2 | 8 | 83:17 | 63:37 | 29 | |
| 6[b] |  **1.72** | 1 | 8 | n.d. | 79:21 | 45 | 10.4 |
| | | 2 | 8 | n.d. | 84:16 | 49 | |
| 7 |  **1.73** | 1 | 8 | 90:10 | 62:38 | 23 | 11.6 |
| | | 2 | 8 | 90:10 | 64:36 | 26 | |

[a] Enantiomer ratios were determined by GC or SFC analysis on chiral stationary phase. [b] Determined by $^1$H NMR analysis. *c* Conv=[*ee***B**/(*ee***B**+*ee***A**)]. [d] *s*=*k*fast/*k*slow=ln[(1-Conv/100)(1-*ee***B**/100)]/ln[(1-Conv/100)(1+*ee***B**/100)].

Aromatic propargyl acetates also led to efficient resolutions under the optimized reaction conditions (Table 1.6). Phenyl substituted propargyl acateate **1.74** led to an average selectivity factor of 11.5. Substitution on the ring and heteroaromatic rings were tolerated but led to slightly diminished selectivities (entry 2-6).

**Table 1.6: Kinetic Resolution of Aromatic Propargyl Acetates**

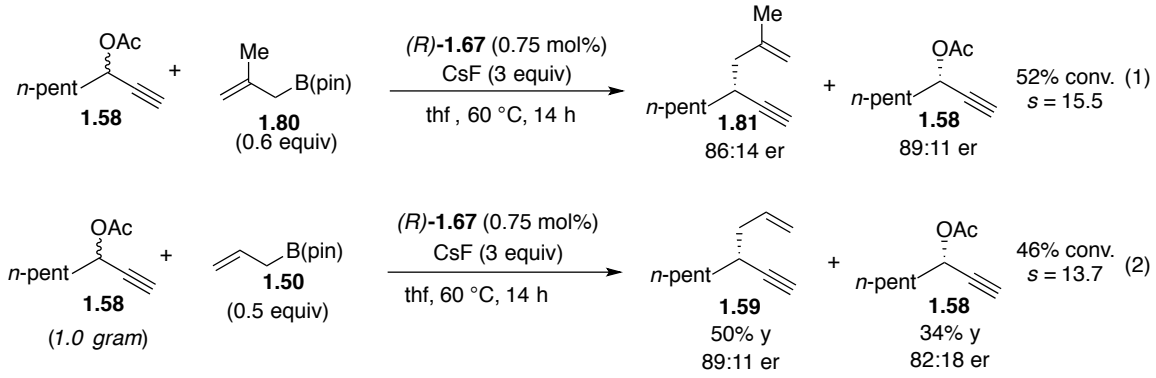



| entry | substrate | no. | t (h) | er **A**[a] | er **B**[a] | conv(%)[b] | $s_{AVG}$[d] |
|---|---|---|---|---|---|---|---|
| 1 |  **1.74** | 1 | 2 | 85:15 | 13:87 | 52 | 11.5 |
| | | 2 | 2 | 86:14 | 22:78 | 44 | |
| 2 |  **1.75** | 1 | 2 | 82:18 | 73:27 | 41 | 7.1 |
| | | 2 | 2 | 82:18 | 72:28 | 41 | |
| 3 |  **1.76** | 1 | 2 | 85:15 | 78:22 | 45 | 10.3 |
| | | 2 | 2 | 88:12 | 72:28 | 37 | |
| 4 |  **1.77** | 1 | 1 | 80:20 | 81:19 | 48 | 7.8 |
| | | 2 | 1 | 82:18 | 81:19 | 47 | |
| 5 |  **1.78** | 1 | 1 | 76:24 | 21:79 | 53 | 5.0 |
| | | 2 | 1.5 | 68:32 | 88:12 | 67 | |
| 6 |  **1.79** | 1 | 2 | 84:16 | 75:25 | 42 | 9.4 |
| | | 2 | 2 | 84:16 | 82:18 | 48 | |

[a] Enantiomer ratios were determined by GC or SFC analysis on chiral stationary phase. [b] Determined by $^1$H NMR analysis. *c* Conv=[*ee***B**/(*ee***B**+*ee***A**)]. [d] *s*=*k*fast/*k*slow=ln[(1-Conv/100)(1-*ee***B**/100)]/ln[(1-Conv/100)(1+*ee***B**/100)].

To widen the scope of the reaction, methallylB(pin) **1.80** was used as the nucleophile in the kinetic resolution and led to nearly the same results as allylB(pin) (Scheme 1.17, eq. 1). To demonstrate the synthetic utility of the reaction, the resolution of **1.58** was carried out on gram scale. The product 1,5-enyne and recovered acetate were isolated in high yields and moderate enantioselectivities with similar selectivity factor as the small scale reaction (Scheme 1.17, eq. 2).

**Scheme 1.17: Application of Other Nucleophiles and Large Scale Kinetic Resolution**




### *1.3.3. Investigation into Mechanism and Origins of Selectivity*

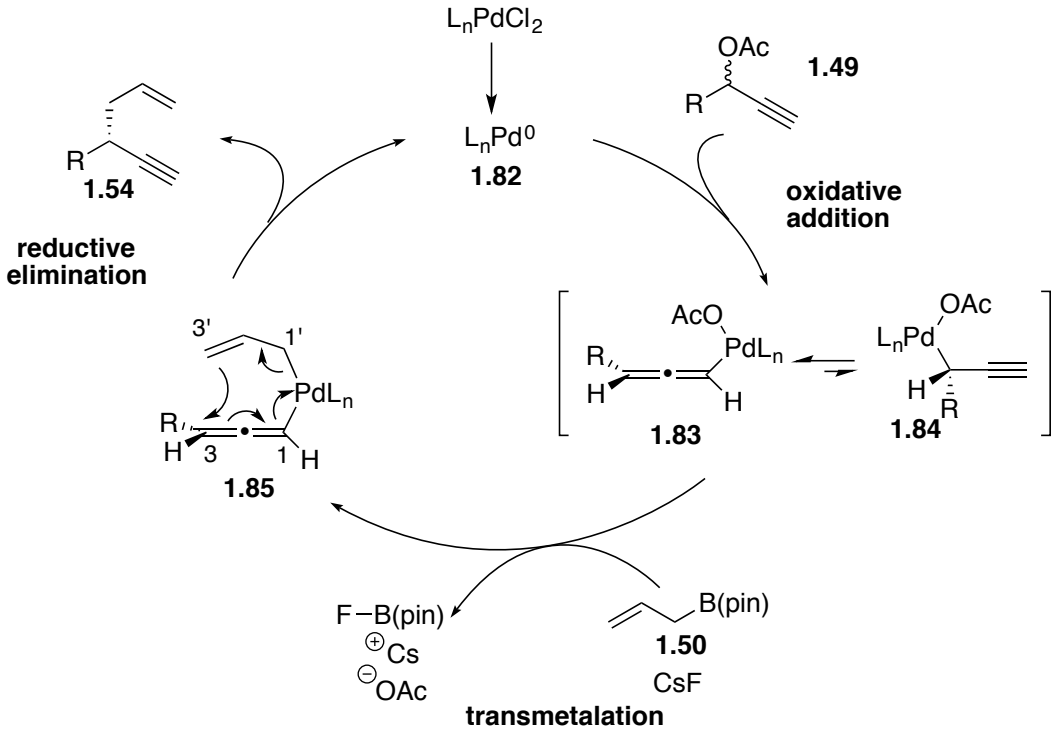
Throughout the optimization of the kinetic resolution, it was apparent that increasing the rate of the oxidative addition, with more electron-rich phosphine or better leaving groups led to decreased selectivity factors. This indicated that the stereochemistry determining step could be oxidative addition. In addition, the use of methallylB(pin) **1.80** in place of allylB(pin) **1.50** as the nucleophile resulted in nearly the

same selectivity factors; suggesting that the nucleophile is not involved in the stereochemistry determining step.

To further probe the origins of selectivity in this resolution, deuterium labeled *d*-**1.58** was prepared and subjected to the resolution in order to probe a secondary kinetic isotope effect. If oxidative addition were indeed the rate-determining step, the hybridization change from sp to $sp^2$ at the alkyne should result in an inverse secondary isotope effect (Scheme 1.18).[31] If the rate-determining step were transmetalation (**1.83** to **1.85**) then no KIE would be observed because the hybridization at the labeled position would not change. Finally, if reductive elimination and product release were stereodefining the result would be a normal secondary isotope effect due to the $sp^2$ to sp hybridization change.

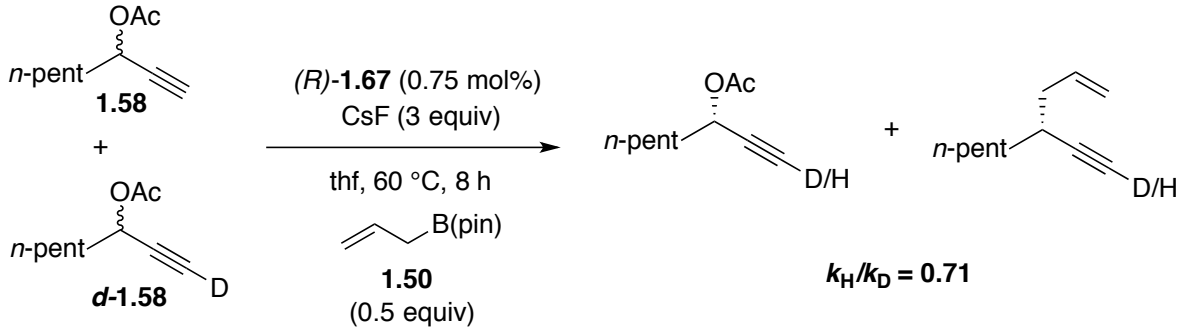
[31] (a) Mucsi, Z.; Szabo, A.; Mermecz, I.; Kucsman, A.; Csizmadia, I. *J. Am. Chem. Soc.* **2005**, *127*, 7615. (b) Arndt, M.; Salih, K.; Fromm, A.; Goossen, L.; Menges, F.; Schatteburg-Niedner, G. *J. Am. Chem. Soc.* **2011**, *133*, 7428.

**Scheme 1.18: Proposed Mechanism of Propargyl Allyl Cross-Coupling**




A mixture of unlabeled **1.58** and labeled ***d*-1.58** were compared by a competition study, where an average $k_H/k_D$ of 0.70 was calculated. This inverse secondary kinetic isotope effect, indicates that oxidative addition is irreversible and therefore the stereochemistry-determining step, but not necessarily the rate-determining step.

**Scheme 1.19: Labeling Studies to Probe Kinetic Isotope Effects**



To better understand the catalyst/substrate interactions during oxidative addition that lead to differences in rate between enantiomers of propargyl acetate DFT studies were carried out by a Morken group member, Dr. Michael Ardolino. To simplify the calculations methyl substituted propargyl acetate **1.86** was used in place of the pentyl **1.58**. The reaction pathway was calculated for each enantiomer of electrophile **1.86** with *(R)*-**L1.6** at 60 °C. The results indicate that the diastereometric ground states of the fast and slow reacting enantiomer upon oxidative addition differ by over 2.0 kcal/mol. Figure 1.1 shows the calculated reaction coordinate and three-dimensional representations of the ground state leading to oxidative addition (**$GS_{fast}$**, **$GS_{slow}$**). Looking closely at these figures, the origin of this energy different is apparent; in the slow reacting enantiomer (S)-**1.86**, the methyl substituent is directly pointing at the equatorial furyl ring, while in the fast reacting (R)- **1.86** it is pointed down and away from the equatorial furyl ring. The $\Delta\Delta G^{\ddagger}$ of 1.3 kcal/mol in the TS favoring reaction with the (*R*)- **1.86** is in agreement with the experimental values. These results provide additional evidence that the stereochemistry defining step of the resolution is likely oxidative addition of the palladium.

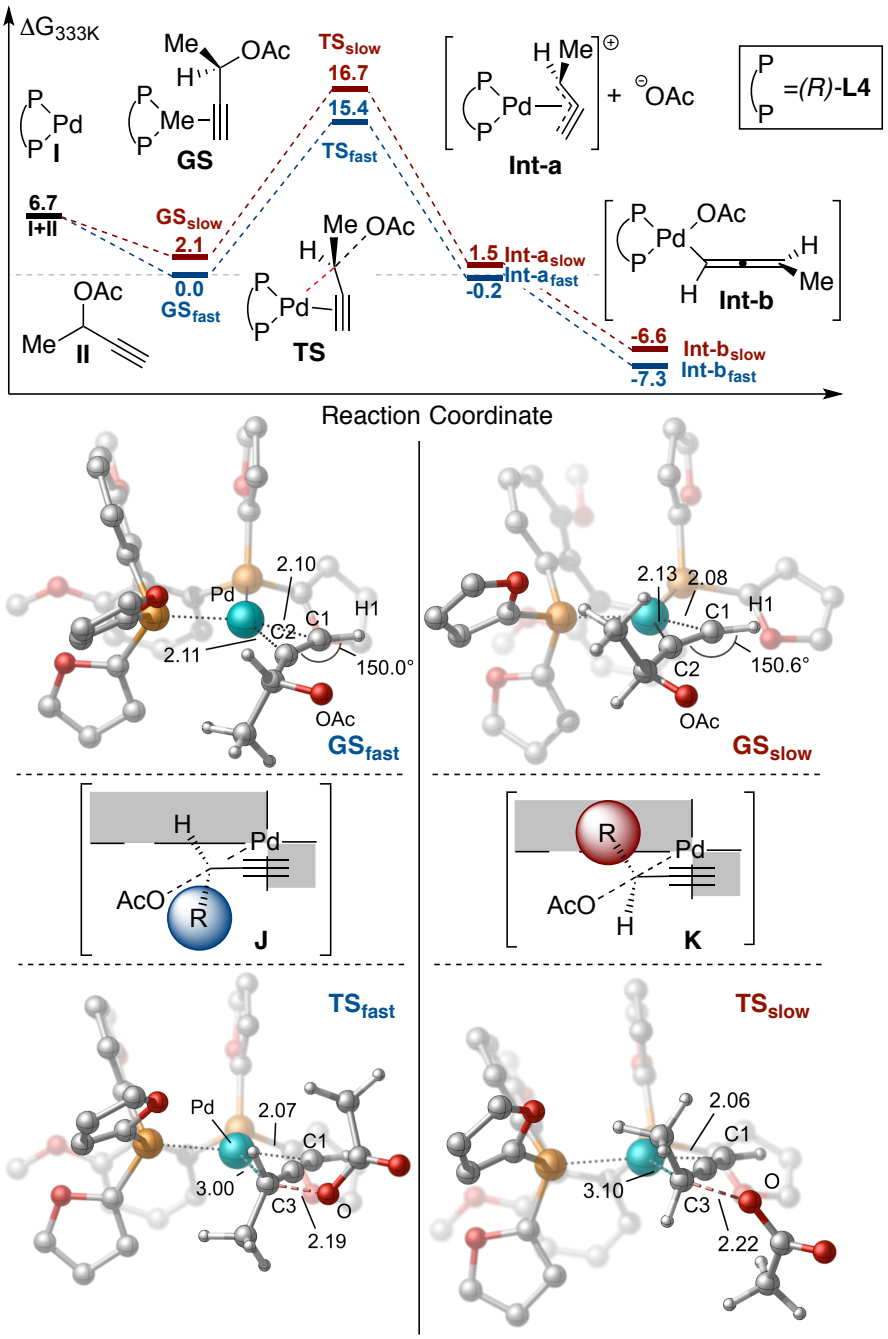



**Figure 1.1:** DFT optimized structures, reaction coordinate and simplified stereochemical model for oxidative addition [Pd] into (R)-**1.86** and (S)-**1.86**. Energy values reported in kcalmol$^{-1}$ relative to **GS$_{fast}$**. Calculations performed at the B3LYP-PCM(THF)/LANL2DZ-6-31G**, some hydrogen atoms removed for clarity.

## 1.4 Development of Pd-Catalyzed Resolution of Propargyl Electrophiles

*1.4.1. Introduction to Dynamic Kinetic Resolution and Application to 1,5-Enyne Synthesis*

After development of the KR of propargyl electrophiles, we considered that perhaps this system could be amenable to a dynamic kinetic resolutions (DKR). Dynamic kinetic resolutions are arguably the most useful type of resolution as all of the racemic starting material can be converted into enantiopure product.[32] This occurs by an *in situ* equilibration of the starting material by a racemization process that has a rate faster than the rate of the reaction, thus allowing all the starting material to funnel to the faster reacting enantiomer (Figure 1.2).

[32] For reviews on dynamic kinetic resolutions see: (a) Bäckvall, J.-E.; Minidis, A.; Huerta, F.F. *Chem. Soc. Rev.* **2001**, *30*, 321. (b) Ward, R.S.; *Tetrahedron: Asymmetry*. **1995**, *6*, 1475. (c) Nunami, K.-N.; Kubota, H.; Kubo, A. *Tet. Lett.* **1994**, 35, 8639.(d) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* ***1995,*** *68, 36. (e)* Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* ***1989****, 111, 9134*

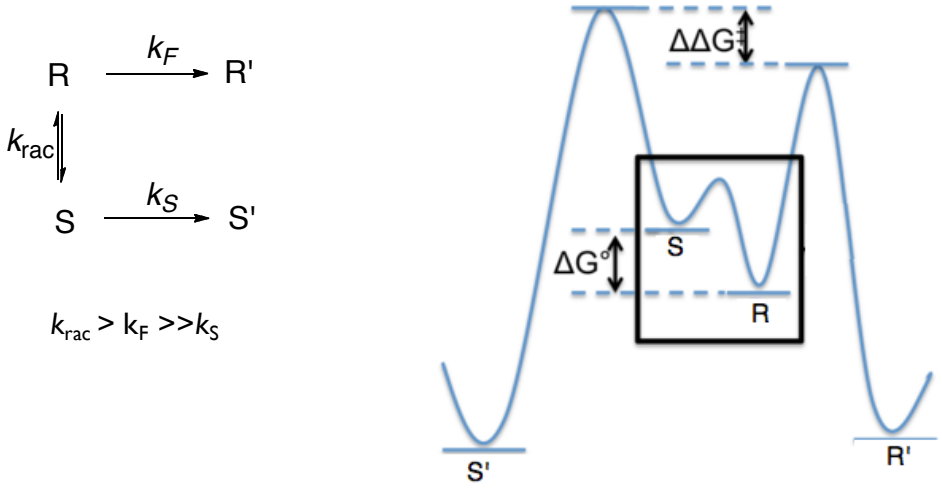


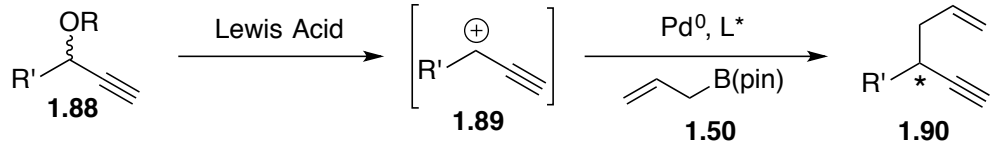

**Figure 1.2: Dynamic Kinetic Resolutions**

Some strategies for *in situ* equilibration can occur by several pathways: base catalyzed racemization via enolate formation reaction, through a planar $sp^2$ intermediate, Schiff base formation, formation of π-allyl intermediates or enzyme catalyzed racemization.[33] 1,5-Enynes are commonly accessed by stoichiometric or catalytic Lewis acid activated allylations of propargyl electrophiles (*vide supra*).[2] These reactions are proposed to proceed through an achiral carbocation intermediate, and result in racemic product. Using the achiral carbocation intermediate as a way to equilibrate the starting material enantiomers, selective oxidative addition of a chiral

[33] For examples of previous DKR see: (a) Trost, B.M.; Toste, F. D.; *J. Am. Chem. Soc.*, **1999**, *121*, 3543. (b) Y. Blum, D. Czarkle, Y. Rahamin and Y. Shvo, *Organometallics, **1985***, 4, 1459. (c) Bäckvall, J.-E.; Larssonn, A.L.E.; Persson, B. A. *Angew. Chem. Ed. Engl.* **1997**, *36*, 1211

palladium catalyst followed by cross-coupling with allyl nucleophiles could result in a DKR (Scheme 1.20).

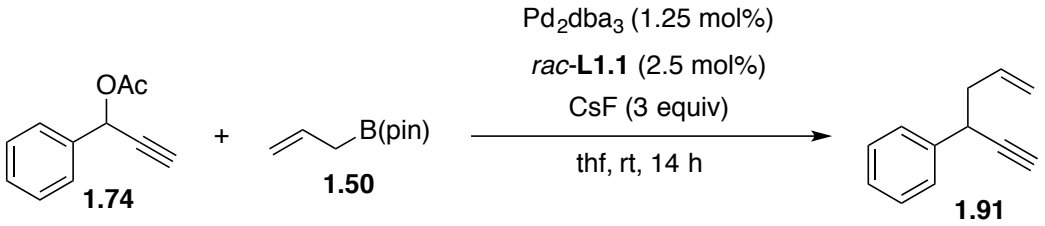
**Scheme 1.20: Proposed DKR of Propargyl Electrophiles *via* Allyl Propargyl Cross-Coupling**




*1.4.2. Optimization of Dynamic Kinetic Resolution*

Using the conditions for allyl-propargyl cross-coupling previously developed by Morken et al.[18], a number of commonly used Lewis acid activators were tested with propargyl acetate **1.74** (Table 1.7). The highest conversions were observed with tris(pentafluorophenyl)borane (FAB), the same catalyst that was used previously by Gevorgyan and co-workers (*vide supra*).[17] Since catalytic amounts of this Lewis acid could be used to activate the leaving group, it seemed to be the ideal additive for the reaction.

**Table 1.7: Screening of Lewis Acids for Dynamic Kinetic Resolution**



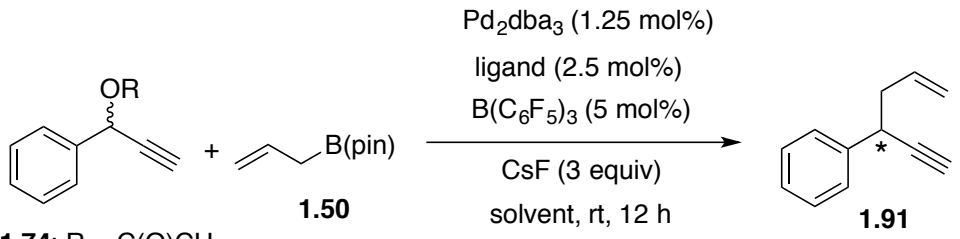

| entry | additive (mol %) | conversion (%) |
|---|---|---|
| 1 | LiCl (100%) | 0 |
| 2 | ZnCl (100%) | 0 |
| 3 | $B(C_6H_5)_3$ (5%) | 13 |
| 4 | $B(C_6F_5)_3$ (5%) | 19 |

The reaction was carried out using 0.10 mmol **1** and 1.2 equivalents of **1.50** in tetrahydrofuran (0.5M). Conversion calculated based on starting material using $^1$H-NMR

We were interested in using chiral ligands in our system. When using chiral bidentate phosphine ligands, we discovered that both the product and recovered propargyl acetate **1.74** were enantioenriched (Table 1.8, entry 1 ,2). One possible reason for the enrichment of the propargyl acetate **1.74** is that oxidative addition is faster than the formation of the carbocation intermediate, and the reaction proceeds through a non-dynamic resolution instead. We predicted that changing to a better leaving group could enhance the rate of carbocation formation and avoid the background kinetic resolution. Changing to chloroacetate **1.92** led to full conversion of the starting material with the product isolated in low enantioselectivity (entry 3). Stopping the reaction halfway, by addition of only 0.5 equiv. of **1.50**, revealed the starting material was still being resolved (entry 4). Further

optimization revealed that the use of phenyl carbamate **1.93** in dichloromethane can favor the DKR, with the starting material recovered in only 6% ee (entry 7).

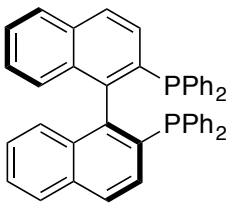
**Table 1.8: Optimization of Dynamic Kinetic Resolution**



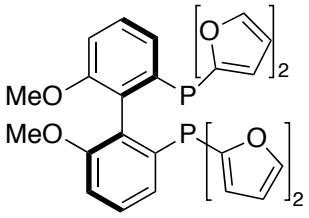

**1.74**: R = $C(O)CH_3$
**1.92**: R = $C(O)CH_2Cl$
**1.93**: R = $CO_2Ph$

| entry | substrate | ligand | solvent | conversion (%) | *ee* (%) **1.91** | *ee* (%) rsm |
|---|---|---|---|---|---|---|
| 1 | 1a | *(S)*-**L1.1** | THF | 39 | 14 | 14 |
| 2 | 1a | *(R)*-**L1.6** | THF | 70 | 20 | 96 |
| 3 | 1b | *(R)*-**L1.6** | THF | 100 | 8 | -- |
| 4[a] | 1b | *(R)*-**L1.6** | THF | 57 | 6 | 36 |
| 5 | 1b | *(R)*-**L1.6** | DCM | 31 | 40 | 2 |
| 6 | 1c | *(R)*-**L1.6** | DCM | 100 | 84 | -- |
| 7[a] | 1c | *(R)*-**L1.6** | DCM | 46 | 80 | 6 |

Conversion calculated based on starting material using $^1$H-NMR. Enantiomeric excesss determined by GC analysis on a chiral stationary phase. [a] Reaction run using 0.5 equivalents of **1.50**.



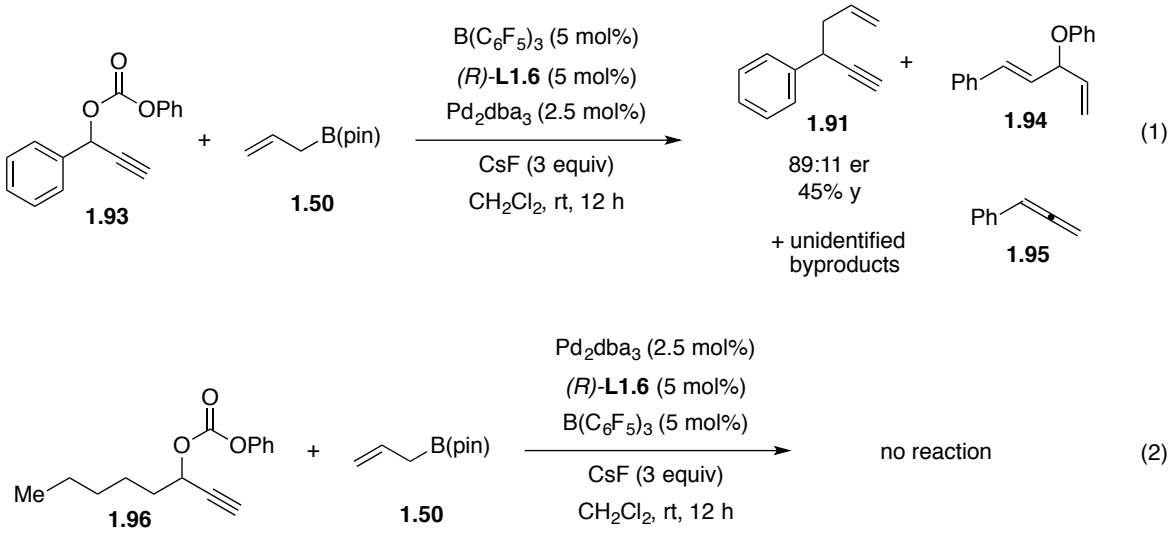

*(S)*-**L1.1**




*(R)*-**L1.6**

Though the use of electrophile **1.93** lead to full consumption of the starting material, there were a number of byproducts formed and the desired 1,5-enyne **1.91** was isolated in only 45% yield (Scheme 4, eq. 1). Attempts to suppress byproduct formation with other carbonate derivatives, led to low reactivity or low enantioselectivites. Furthermore, aliphatic substrates proved to be poor substrates due to reduced stability of the carbocation (Scheme 1.21, eq. 2). Since the scope of the already developed kinetic resolution was broader than the proposed DKR, we decided not to further pursue the development of this method.

**Scheme 1.21: Results of DKR with Different Electrophiles Under Optimized Condtions**




## 1.5 Conclusion

To summarize, we had identified a slight matched/mismatched catalyst/substrate interaction during the development of a stereospecific propargyl allyl cross-coupling that

allowed us to develop a kinetic resolution. During the development of this kinetic resolution, small byproduct formation and non-reproducible selectivity factors led us to investigate pre-catalysts other than $Pd_2dba_3$. The use of Pd(II)-ligand complex *(R)*-**1.67** allowed for a clean reaction and significantly decreased catalyst loadings. The reaction could then be expanded to include aromatic and aliphatic electrophiles as well as methallyB(pin) nucleophiles. Mechanistic experiments support oxidative addition as the rate- and stereodefining step in the resolution. This development, at the time, represented the first method to access enantioenriched 1,5-enynes from racemic propargyl electrophiles. We also showed that this transformation could be accomplished through at DKR of propargyl carbamates with Lewis acid additives, however this method has not been fully developed.

## 1.6 Experimental

### *1.6.1. General Information*

$^1$H NMR spectra were recorded on a Varian Gemini-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet, app = apparent), and coupling constants (Hz). Coupling constants are reported to the nearest 0.5 Hz. $^{13}$C NMR spectra were recorded on a Varian Gemini-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent

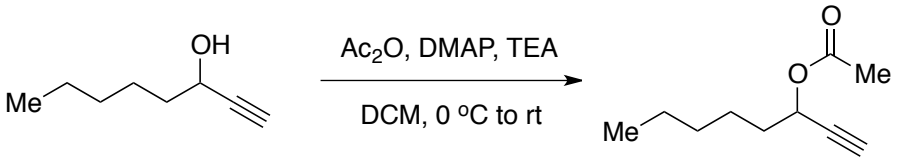
resonance as the internal standard ($CDCl_3$: 77.0 ppm). $^{31}P$ NMR spectra were recorded on a Varian Gemini-500 (202 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with phosphoric acid as the external standard ($H_3PO_4$: 0.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer, $\upsilon_{max}$ $cm^{-1}$. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High resolution mass spectrometry (ESI) was performed at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel ($SiO_2$, 230×450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate ($KMnO_4$) in water, ceric ammonium molybdate (CAM) in water, or phosphomolybdic acid (PMA) in ethanol. Analytical chiral gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, a flame ionization detector, and a Supelco β-Dex 120 column, or a Supelco Asta Chiraldex B-DM with helium as the carrier gas. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar SFC equipped with a Waters 2998 photodiode array detector and an analytical-2-prep column oven with isopropanol or a 1:1 mixture of isopropanol:hexanes and as the modifier. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF), dichloromethane (DCM) and toluene (PhMe) were purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. by passing through two activated alumina columns after being purged with argon. Triethylamine was distilled from calcium hydride. Tris(dibenzylideneacetone) dipalladium(0) [$Pd_2(dba)_3$], bis(benzonitrile)palladium(II) chloride, 1,2-bis(diphenylphosphino)benzene, *(R)*-(+)-2,2′-bis(di-2-furanylphosphino)-6,6′-dimethoxy-1,1′-biphenyl [*(R)*-MeO(furyl)BIPHEP], *(S)*-(+)-2,2′-bis(di-2-furanylphosphino)-6,6′-dimethoxy-1,1′-biphenyl [*(S)*-MeO(furyl)BIPHEP],, and (*R*,*R*)-(−)-2,3-Bis(*t*-butylmethylphosphino)quinoxaline [(*R*,*R*)-QuinoxP*] were purchased from Strem Chemicals, Inc. Allylboronic acid pinacol ester (allyl Bpin) was generously donated by Frontier Scientific. Bis(pinacolato) diboron [$B_2(pin)_2$] was generously donated by Allychem. All other reagents were purchased from either Fisher or Aldrich and used without further purification.

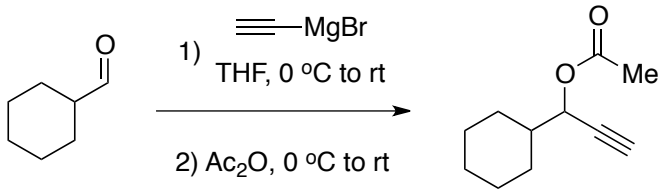
### *1.6.2. Experimental Procedures*

#### *1.6.2.1 Preparation of Substituted Propargyl Acetates*




**Representative Procedure A (1.58):** An oven-dried round-bottomed flask equipped with

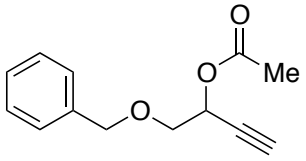
a magnetic stir bar was charged with dichloromethane (20.0 mL), 1-octyn-3-ol (500 mg, 3.96 mmol), and dimethylamino pyridine (catalytic) under nitrogen atmosphere. The solution was cooled to 0 °C and triethylamine (1.2 g, 11.9 mmol) was added, followed by dropwise addition of acetic anhydride ((484.9 mg, 4.7 mmol). The solution was gradually warmed to room temperature and stirred for 2 h. The reaction was concentrated *in vacuo*, and the crude reaction mixture was purified on silica gel (10:1 pentane:diethyl ether) to afford a clear, colorless oil (599 mg, 90% yield). $R_f$ = 0.60 (10:1 pentane:diethyl ether, stain in PMA). Spectral data is in accordance with the literature.[34]



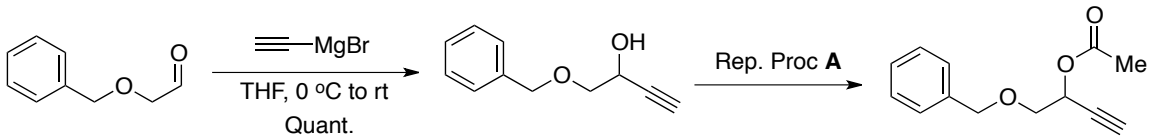

**Representative Procedure B (1.73):** An oven-dried round-bottomed flask equipped with a magnetic stir bar was charged with THF (15 mL) and cyclohexyl carboxaldehyde (336 mg, 3.00 mmol). The solution was cooled to 0 °C and ethynylmagnesium bromide (8.4 mL of a 0.5 M solution in THF, 4.2 mmol) was added dropwise. The solution was stirred for 10 minutes at 0 °C and gradually warmed to room temperature and stirred for 45 minutes. The solution was then cooled to 0 °C and acetic anhydride (432.2 mg, 4.2 mmol) was added dropwise. The solution was allowed to stir for 20 minutes at 0 °C and then gradually warmed to room temperature followed by stirring for one hour. The reaction was

[34] Ghosh, N.; Nayak, S.; Sahoo, A. *J. Org. Chem.* **2011**, *76,* 500.

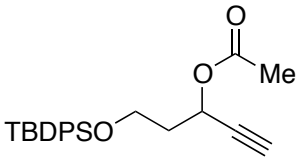
recooled to 0 °C and quenched with saturated aqueous ammonium chloride and extracted three times with diethyl ether. The organic layers were combined, dried over sodium sulfate, concentrated *in vacuo* and purified on silica gel (30:1 hexane:ethyl acetate) to afford a clear, colorless oil (392 mg, 73% yield). $R_f$ = 0.64 (5:1 hexane:ethyl acetate, stain in PMA). Spectral data is in accordance with the literature.[35]



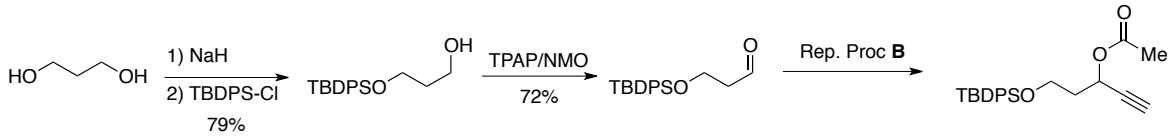
***1-(benzyloxy)but-3-yn-2-yl acetate (Compound 1.68).*** From 1-(benzyloxy)but-3-yn-2-ol, prepared as shown below from commercially available 2-(benzyloxy)acetaldehyde, representative procedure **A** was followed to afford a clear, colorless oil (617 mg, 94% yield). $R_f$ = 0.6 (5:1 pentane:diethyl ether, stain in $KMnO_4$). Spectral data is in accordance with the literature.

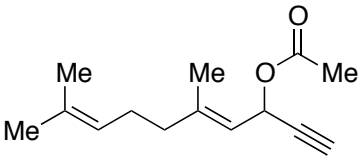



[35] Detz, R.; Abiri, Z.; Griel, R.; Hiemstra, H.; Maarseveen, J. *Chem. Eur. J.* **2011**, *21*, 5921.

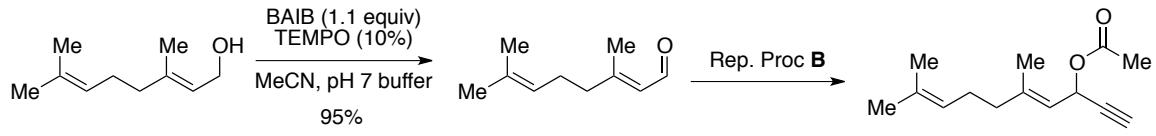


***5-((tert-butyldiphenylsilyl)oxy)pent-1-yn-3-yl acetate (Compound 1.69).*** From 3-((*tert*-butyldiphenylsilyl)oxy)propanal, synthesized as shown below utilizing a two-step procedure from commercially available propane-1,3-diol,– representative procedure **B** was followed to afford a clear, colorless oil (279 mg, 74% yield). $R_f$ = 0.71 (10:1 pentane:diethyl ether, stain in PMA). Spectral data is in accordance with the literature.[36]

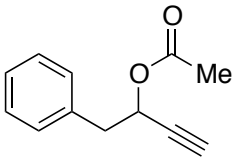


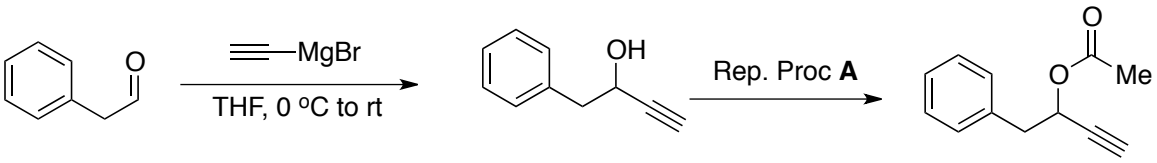
***(E)-5,9-dimethyldeca-4,8-dien-1-yn-3-yl acetate (Compound 1.70).*** From *(E)*-3,7-dimethylocta-2,6-dienal, synthesized as shown below from commercially available geraniol, representative procedure **B** was followed to afford a clear, colorless oil (821 mg, 93% yield). $R_f$ = 0.83 (10:1 pentane:diethyl ether, stain in PMA). Spectral data is in accordance with the literature.[37]

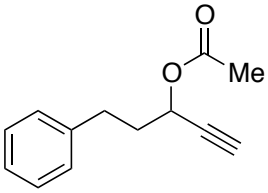



[36] Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 8770.

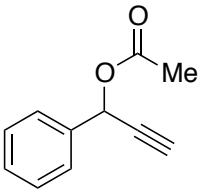


***1-phenylbut-3-yn-2-yl acetate (Compound 1.71).*** From 1-phenylbut-3-yn-2-ol, prepared as shown below from commercially available 2-phenylacetaldehyde, representative procedure **B** was followed to afford a clear, colorless oil (297 mg, 79% yield). $R_f$ = 0.7 (5:1 pentane:diethyl ether, stain in PMA). Spectral data is in accordance with the literature. [35]

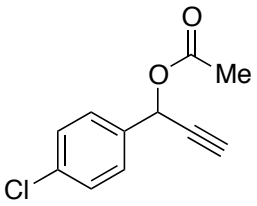


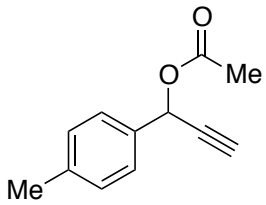
***5-phenylpent-1-yn-3-yl acetate (Compound 1.72).*** From commercially available hydrocinnamaldehyde, representative procedure **B** was followed to afford a clear, colorless oil (763 mg, 88% yield). $R_f$ = 0.80 (5:1 pentane:diethyl ether, stain in PMA). Spectral data is in accordance with the literature. [36]



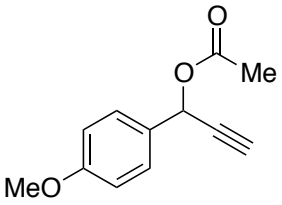
***1-phenylprop-2-yn-1-yl acetate (Compound 1.74).*** From commercially available 1-phenylprop-2-yn-1-ol, representative procedure **A** was followed to afford a clear, colorless oil (938 mg, >96% yield). $R_f$ = 0.39 (10:1 pentane:diethyl ether, stain in PMA). Spectral data is in accordance with the literature. [35]



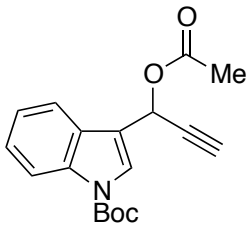

***1-(4-chlorophenyl)prop-2-yn-1-yl acetate (Compound 1.75).*** From commercially available 4-chlorobenzaldehyde, representative procedure **B** was followed to afford a clear, pale yellow oil (574 mg, 92% yield). $R_f$ = 0.32 (10:1 hexane: ethyl acetate, stain in PMA). Spectral data is in accordance with the literature.[35]



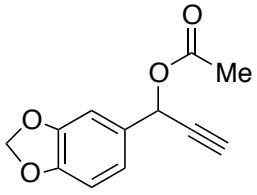

***1-(p-tolyl)prop-2-yn-1-yl acetate (Compound 1.76).*** From commercially available *p*-tolualdehyde, representative procedure **B** was followed to afford a clear, colorless oil (282 mg, >96% yield). $R_f$ = 0.26 (25:1 hexane:ethyl acetate; stain in PMA). Spectral data is in accordance with literature. [35]




***1-(4-methoxyphenyl)prop-2-yn-1-yl acetate (Compound 1.77).*** From commercially available 4-methoxybenzaldehyde, representative procedure **B** was followed. The crude reaction mixture was purified on silica gel (10:1 pentane:diethyl ether) to afford a clear, pale yellow oil (741 mg, >96% yield). $R_f$ = 0.4 (10:1 pentane:diethyl ether; stain in CAM). Spectral data is in accordance with the literature.[36]

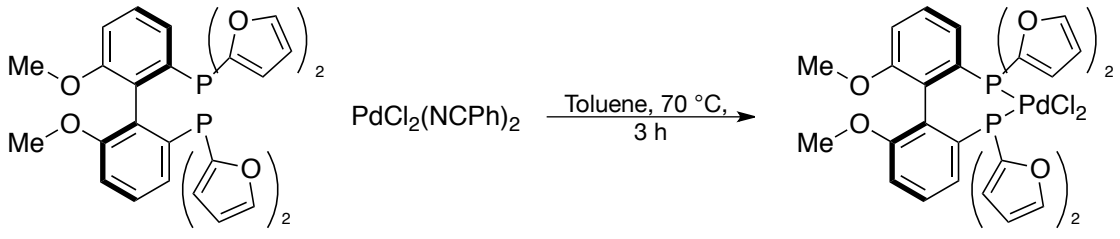


***tert-butyl-3-(1-acetoxyprop-2-yn-1-yl)-1H-indole-1-carboxylate (Compound 1.78).*** From *tert*-butyl 3-formyl-1*H*-indole-1-carboxylate, synthesized as shown below from 1*H*-indole-3-carbaldehyde, representative procedure **B** was followed to afford a pale brown viscous oil (649 mg, 86% yield). $R_f$ = 0.43 (5:1 pentane:diethyl ether, stain in PMA). Spectral data is Spectral data is in accordance with the literature. [37]



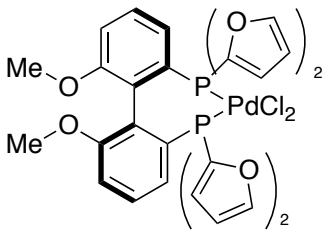
***1-(benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-yl acetate (Compound 1.79).*** From commercially available piperonal, representative procedure **B** was followed to afford a white solid (849 mg, >96% yield). $R_f$ = 0.14 (20:1 hexane: ethyl acetate; stain in PMA). Spectral data is in accordance with the literature.[36]

*1.6.2.2 Preparation of [(R)-(+)-2,2'-Bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl]palladium(II) dichloride (R)-1.67*[37]



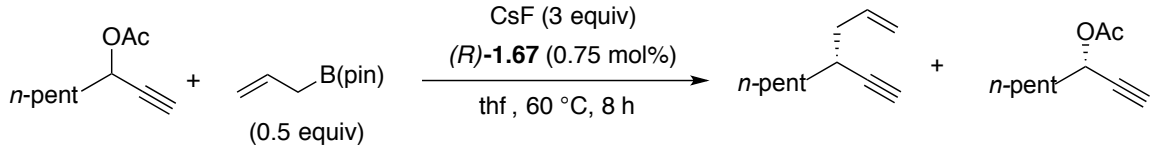

[37] Modified from: Sperrie, M.; Consiglio, G. *J. Am. Chem. Soc.* **1995**, *117*, 12130.

An oven-dried round-bottomed flask equipped with a magnetic stir bar was charged with bis(benzonitrile)palladium(II) chloride (83.9 mg, 0.219 mmol) and toluene (12.0 mL) in a dry-box under argon atmosphere to form a rust-brown solution. Also in the dry-box, an oven-dried 2 dram vial equipped with a magnetic stir bar was charged with *(R)*-(+)-2,2'-Bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl [*(R)*-Methoxy(furyl)BIPHEP] and toluene (3.0 mL). Both vessels were sealed with septa, removed from the dry box, and heated to 70 °C with stirring under a positive pressure of dry nitrogen. The solution of ligand was added dropwise to the stirring solution of palladium complex over five minutes. The solution was stirred for three hours, over the course of which a bright yellow precipitate formed. The solution was slowly cooled to room temperature, and additional solids were crashed out of solution with the addition of 30 mL pentane. The solids were filtered away from the solution in a Buchner funnel with filter paper and washed with cold diethyl ether to yield a fine, dull yellow powder. This powder was dried for 12 hours under high-vacuum at 60 °C to yield a bright yellow powder (106 mg, 67% yield). The catalyst complex was effective without any further purification. [*(S)*-(+)-2,2'-Bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl]palladium(II) dichloride was prepared utilizing the same method with *(S)*-(+)-2,2'-Bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl [*(S)*-Methoxy(furyl)BIPHEP



**[ *(R)*-(+)-2,2'-Bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl]palladium(II) dichloride (1.67)**. $^{1}$H NMR (500 MHz, CDCl3): δ 7.80 (2H, s), 7.483 (2H, s), 7.22 (2H, dd, J = 3.0 Hz, 3.0 Hz), 7.16 (2H, ddd, J = 8.0 Hz, 8.0 Hz, 3.0 Hz), 6.93 (2H, d, J = 3.0 Hz), 6.85 (2H, dd, J = 12.5 Hz, 8.0 Hz), 6.76 (2H, d, J = 8.0 Hz), 6.45 (2H, ddd, J = 3.0 Hz, 1.5 Hz, 1.5 Hz), 6.24-6.43 (2H, m), 3.60 (6H, s); $^{31}$P NMR (202 MHz, $CDCl_3$): δ -11.56; IR (neat): 3109 (m), 3084 (m), 2937 (m), 2835 (w), 2228 (m), 1461 (s), 1267 (s), 1010 (s); A crystal structure of this catalyst complex has also been previously reported.[38]

*1.6.2.3 Representative Procedure for Resolution of Propargyl Acetates with Allylboronic acid Pinacol Ester*



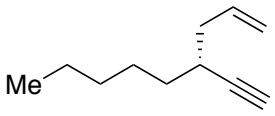

An oven-dried scintillation vial equipped with a magnetic stir bar was charged successively with [*(R)*-(+)-2,2'-Bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl]palladium(II) dichloride (2.16 mg, 3.0 µmol), THF (0.8 mL), oct-1-yn-3-yl acetate (67.3 mg, 0.40 mmol), allylboronic acid pinacol ester (33.6 mg, 0.20 mmol), and cesium fluoride (182.3 mg, 1.2 mmol) in a dry-box under argon atmosphere. The vial was sealed, removed from the dry-box, and heated to 60 °C while allowing to stir for 8 h. After this time, the reaction mixture was diluted with diethyl ether, filtered through a plug of silica

[38] Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778.

gel and concentrated *in vacuo*.

*1.6.2.4 Characterization of Products and Analysis of Stereochemistry*

**Kinetic resolution to give *(R)*-4-ethynylnon-1-ene (Table 1.5, Entry 1):** The representative procedure was followed with oct-1-yn-3-yl acetate.

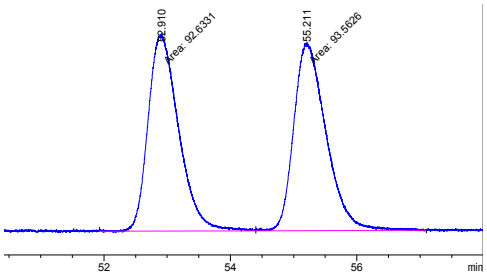



***(R)*-4-ethynylnon-1-ene (Table 1.5, Entry 1 A)**. The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil. $R_f$ = 0.71 (pentane, stain in PMA). $[\alpha]^{22}_D$ = 11.0 (c = 0.20, $CDCl_3$). Spectral data is in accordance with literature.

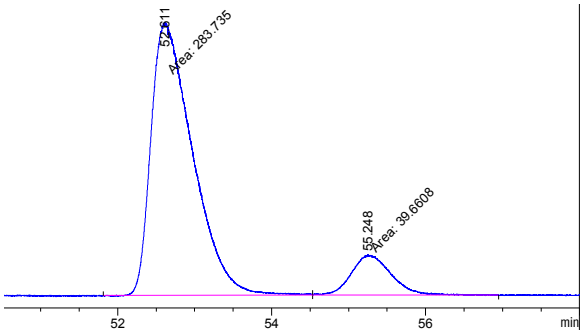
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned as shown below.

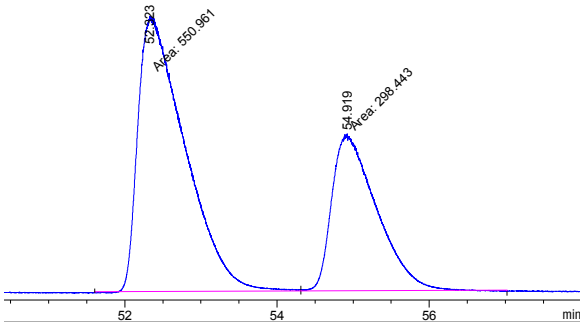
*Chiral GLC (CD-BDM, Supelco, 40 °C for 30 min, ramp 0.25 °C/min to 50 °C for 10 min, 20 psi) - analysis of title compound.*




Racemic Sample




Enantioenriched Sample

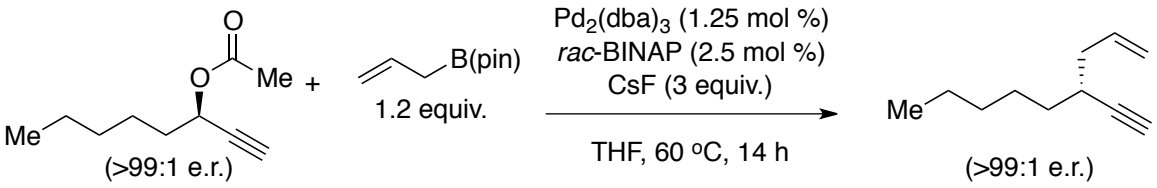



co-injection of racemic and enantioenriched samples

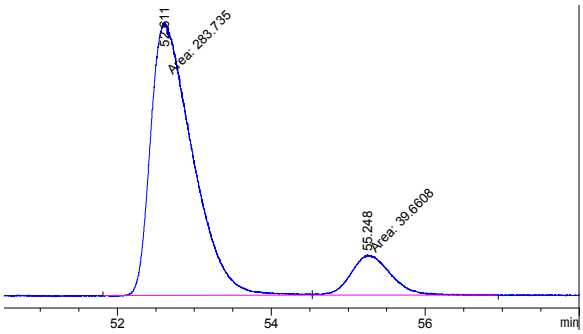
| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 52.611 | MF | 0.6246 | 283.73468 | 7.57123 | 87.73612 |
| 2 | 55.248 | FM | 0.5893 | 39.66084 | 1.12167 | 12.26388 |

***Proof of Absolute Stereochemistry:***

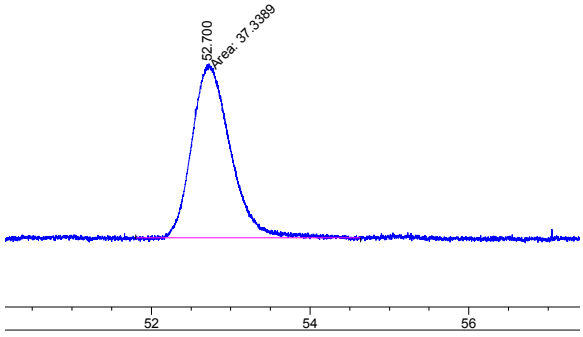
In order to determine the absolute stereochemistry, the title compound was compared by GLC analysis to authentic *(R)*-4-ethynylnon-1-ene, prepared by the stereospecific enyne cross coupling as depicted below. [3]



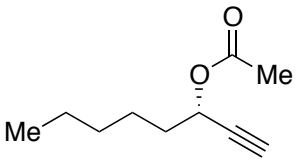
*Chiral GLC (CD-BDM, Supelco, 40 °C for 30 min, ramp 0.25 °C/min to 50 °C for 10 min, 20 psi) - analysis of title compound.*




*Title Compound*




authentic (R)-4-ethynylnon-1-ene

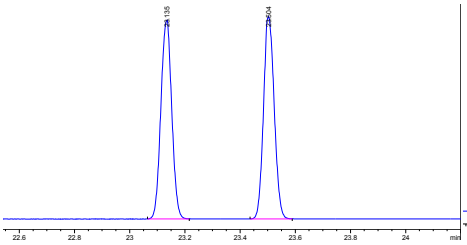



***(S)*-oct-1-yn-3-yl acetate (Table 1.5, Entry 1 B)**. The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil. $R_f$ = 0.60 (10:1 pentane: diethyl ether, stain in PMA). $[\alpha]^{22}_D$ = -19.1 (*c* = 1.06, $CDCl_3$). Spectral data is in accordance with literature. [1]

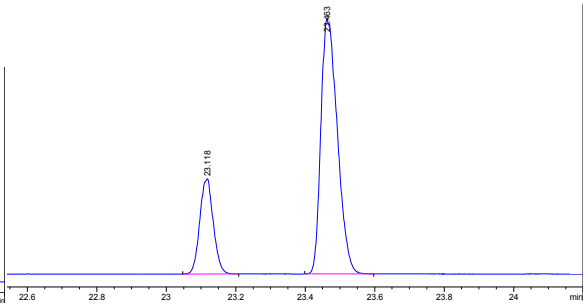
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned as shown below.

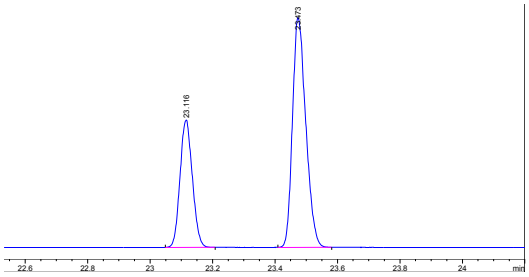
*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 5 °C/min to 140 °C for 10 min, 20 psi) - analysis of title compound.*



Racemic Sample



Enantioenriched Sample

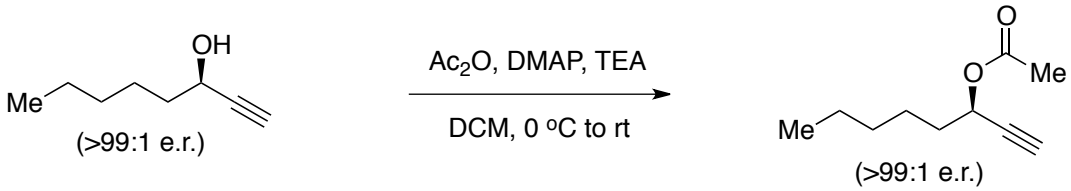


co-injection of racemic and enantioenriched samples

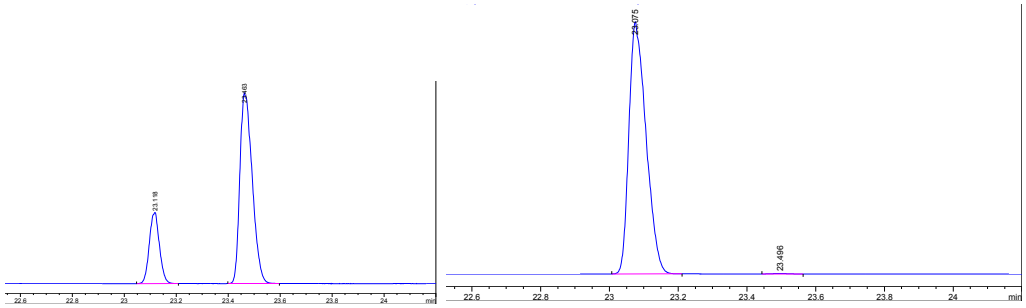
| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 23.118 | BB | 0.0346 | 168.23032 | 62.15095 | 23.41013 |
| 2 | 23.463 | BB | 0.0412 | 550.39166 | 166.93874 | 76.58987 |

***Proof of Absolute Stereochemistry:***

In order to determine the absolute stereochemistry, the title compound was compared by GLC analysis to authentic *(R)*-oct-1-yn-3-yl acetate prepared from commercially available *(R)*-oct-1-yn-3-ol as shown below.

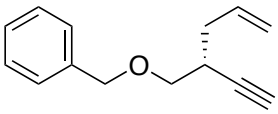


*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 5 °C/min to 140 °C for 10 min, 20 psi) - analysis of title compound.*



*Title Compound* *(R)*-oct-1-yn-3-yl acetate

**Kinetic resolution to give *(R)*-(((2-ethynylpent-4-en-1-yl)oxy)methyl)benzene (Table 1.5, Entry 2):** The representative procedure was followed with 1-(benzyloxy)but-3-yn-2-yl acetate on a 0.2 mmol scale.



***(R)*-(((2-ethynylpent-4-en-1-yl)oxy)methyl)benzene (Table 1.5, Entry 2 A)**. The crude reaction mixture was purified on silica gel (10:1 pentane:diethyl ether) to afford a clear, colorless oil. $R_f$ = 0.86 (10:1 pentane:diethyl ether, stain in $KMNO_4$). $[\alpha]^{22}_D$ = -8.461 (c = 0.73, $CHCl_3$). Spectral data is in accordance with the literature.[37]

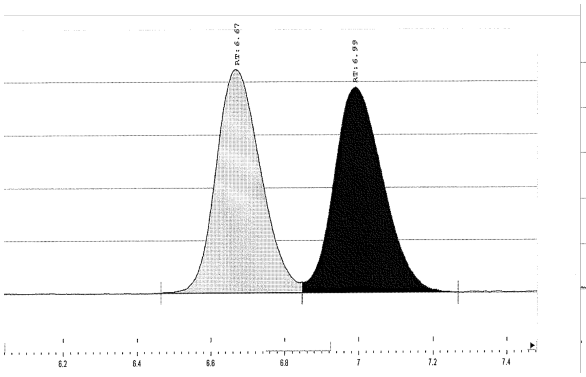
***Analysis of Stereochemistry:***

Optical purity was determined by SFC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-4-

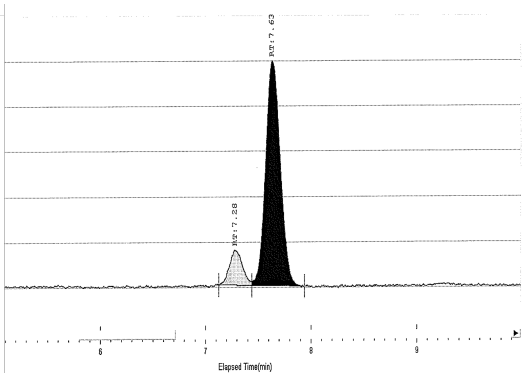
ethynylnon-1-ene (Table 1.5, Entry 1 A).

*Chiral SFC (OJ-H, Chiralpak, 215 nm, 1.0 mL/min, 1.0% 1:1 i-PrOH:Hexanes, 100 bar, 35 °C)*

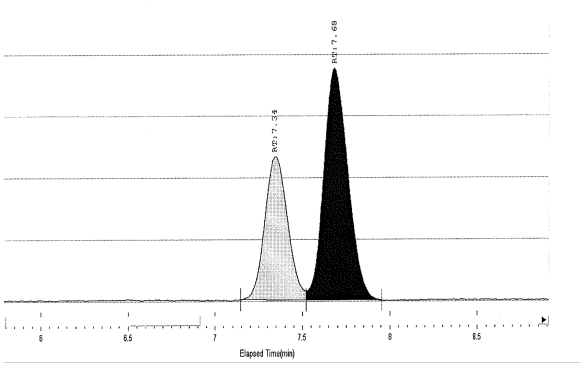
*- analysis of title compound.*




Racemic Sample

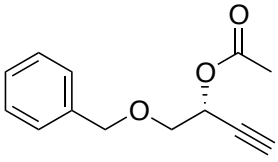



Enantioenriched Sample




| Peak No | % Area | Area | RT (min) |
|---|---|---|---|
| 1 | 12.1609 | 133.3423 | 7.28 |
| 2 | 87.8391 | 963.1384 | 7.63 |
| Total: | 100 | 1096.4807 | |

co-injection of racemic and enantioenriched samples



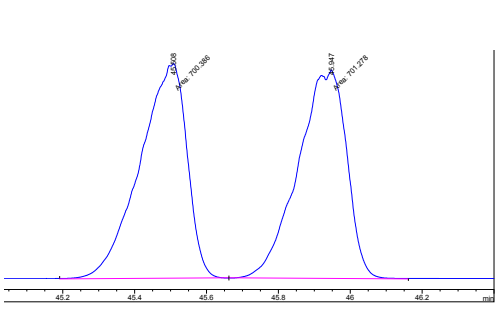
***(R)*-1-(benzyloxy)but-3-yn-2-yl acetate (Table 1.5, Entry 2 B)**. The crude reaction mixture was purified on silica gel (10:1 pentane:diethyl ether) to afford a clear, colorless oil. $R_f$ = 0.24

(10:1 pentane:diethyl ether, stain in $KMnO_4$). $[\alpha]^{22}_D$ = -28.4 (*c* = 10.76, $KMNO_4$). Spectral data is in accordance with the literature.[35]

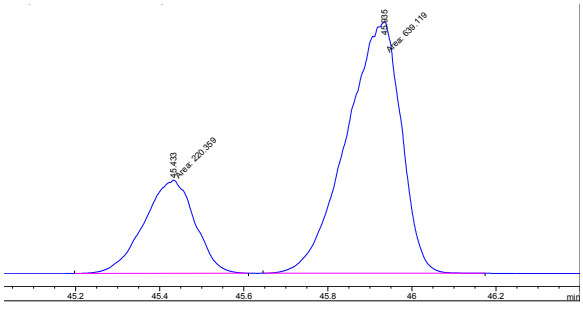
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(S)*-oct-1-yn-3-yl acetate (Table 1.5, Entry 1B).

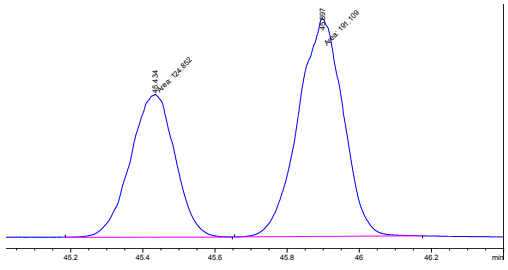
*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 5 °C/min to 160 °C for 20 min, 20 psi) - analysis of title compound.*



Racemic Sample



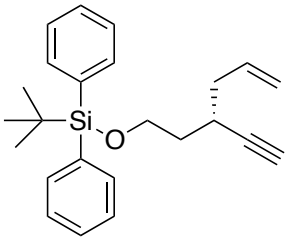
Enantioenriched Sample



co-injection of racemic and enantioenriched samples

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 45.433 | MM | 0.1399 | 220.35901 | 26.25463 | 25.63870 |
| 2 | 45.935 | MM | 0.1506 | 639.11896 | 70.73759 | 74.36130 |

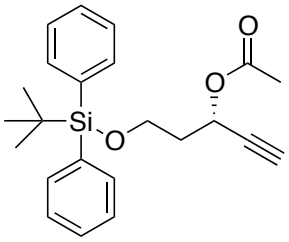
**Kinetic resolution to give *(S)*-tert-butyl((3-ethynylhex-5-en-1-yl)oxy)diphenylsilane (Table 1.5, Entry 3):** The representative procedure was followed with 5-((tert-butyldiphenylsilyl)oxy)pent-1-yn-3-yl acetate with the following modification: the reaction was run for 12 hours on a 0.2 mmol scale.




***(S)*-tert-butyl((3-ethynylhex-5-en-1-yl)oxy)diphenylsilane (Table 1.5, Entry 3A)**. The crude reaction mixture was purified on silica gel (10:1 pentane:diethyl ether) to afford a clear, colorless oil. $R_f$ = 0.95 (10:1 pentane:diethyl ether, stain in $KMnO_4$). $[\alpha]^{22}_D$ = 14.0 (c = 1.52, $CHCl_3$). Spectral data is in accordance with the literature.[37]

***Analysis of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to *(R)*-4-ethynylnon-1-ene (Table 1.5, Entry 1A).

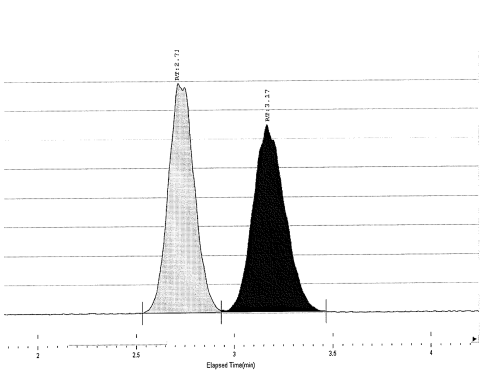



***(S)*-5-((tert-butyldiphenylsilyl)oxy)pent-1-yn-3-yl acetate (Table 5.1, Entry 3B)**. The crude reaction mixture was purified on silica gel (10:1 pentane:diethyl ether) to afford a clear, colorless oil. $R_f$ = 0.35 (10:1 pentane:diethyl ether, stain in $KMnO_4$). $[\alpha]^{22}_D$ = -18.1 (c = 1.52, $CHCl_3$). Spectral data is in accordance with the literature.

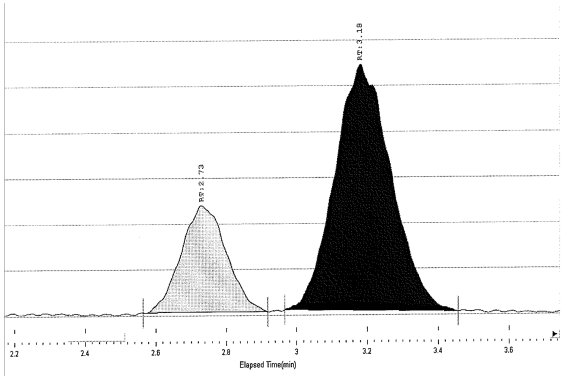
***Analysis of Stereochemistry:***

Optical purity was determined by SFC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(S)*-oct-1-yn-3-yl acetate (Table 1.5, Entry 1B).

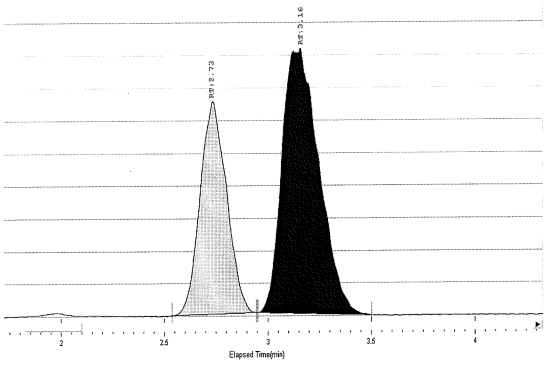
*Chiral SFC (OJ-H, Chiralpak, 215 nm, 5.0 mL/min, 1.0% 1:1 i-PrOH:Hexanes, 100 bar, 35 °C) - analysis of title compound.*




Racemic Sample




Enantioenriched Sample

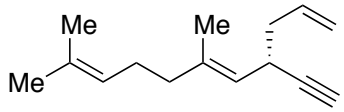



co-injection of racemic and enantioenriched samples

| Peak Info | | | | | |
|---|---|---|---|---|---|
| Peak Name | Number | Concentration | Area % | Area | Area Sum |
| Peak1 | 1 | 0 | 25.8179 | 1036.9514 | |
| Peak2 | 2 | 0 | 74.1821 | 2979.4555 | 4016.407 |

| RT (min) | St. (min) | End (min) | Height |
|---|---|---|---|
| 2.73 | 2.5644 | 2.9162 | 116.5486 |
| 3.18 | 2.9661 | 3.4545 | 268.681 |

**Kinetic resolution to give *(S,E)*-4-ethynyl-6,10-dimethylundeca-1,5,9-triene (Table 1.5, Entry 4):** The representative procedure was followed with *(E)*-5,9-dimethyldeca-4,8-dien-1-yn-3-yl acetate with the following modification: the reaction was run for 1.5 hours at 0.5% catalyst loading on a 0.2 mmol scale.

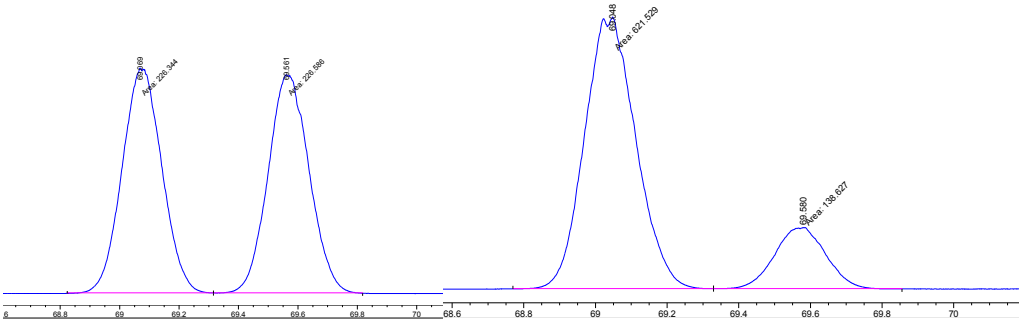



***(S,E)*-4-ethynyl-6,10-dimethylundeca-1,5,9-triene (Table 1.5, Entry 4A)**. The crude reaction mixture was purified on silica gel (20:1 pentane: diethyl ether) to afford a clear, pale yellow oil. $R_f$ = 0.97 (20:1 pentane: diethyl ether, stain in $KMNO_4$). $[\alpha]^{22}_D$ = 32.5 (c = 0.79, $CHCl_3$). Spectral data is in accordance with the literature. [37]

***Analysis of Stereochemistry:***

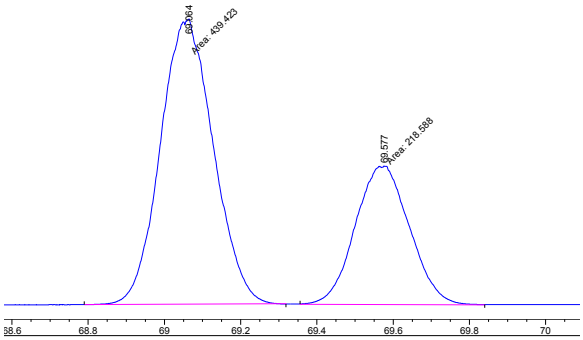
Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-4-ethynylnon-1-ene (Table 1.5, Entry 4A).

*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 1 °C/min to 140 °C for 40 min, 20 psi) - analysis of title compound.*



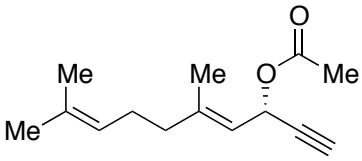

Racemic Sample

Enantioenriched Sample




| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 69.048 | MM | 0.1661 | 621.52887 | 62.35764 | 81.76338 |
| 2 | 69.580 | MM | 0.1646 | 138.62669 | 14.03614 | 18.23662 |

co-injection of racemic and enantioenriched samples



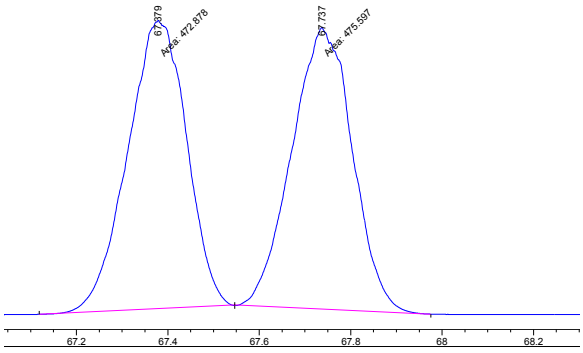

***(S,E)*-5,9-dimethyldeca-4,8-dien-1-yn-3-yl acetate (Table 1.5, Entry 4B)**. The crude reaction mixture was purified on silica gel (20:1 pentane: diethyl ether) to afford a clear, pale yellow oil. $R_f$ = 0.49 (20:1 pentane: diethyl ether, stain in $KMnO_4$). $[\alpha]^{22}_D$ = 15.5 (c = 1.12, $CHCl_3$). Spectral data is in accordance with the literature.[37]

***Analysis of Stereochemistry:***

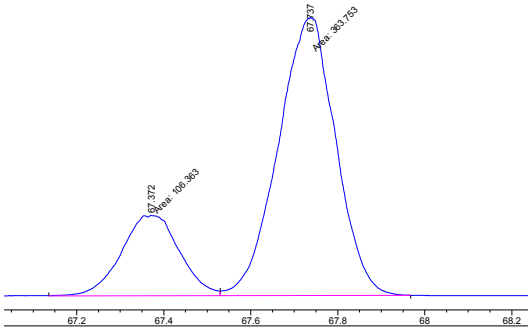
Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(S)*-oct-1-

yn-3-yl acetate (Table 1.5, Entry 1B).

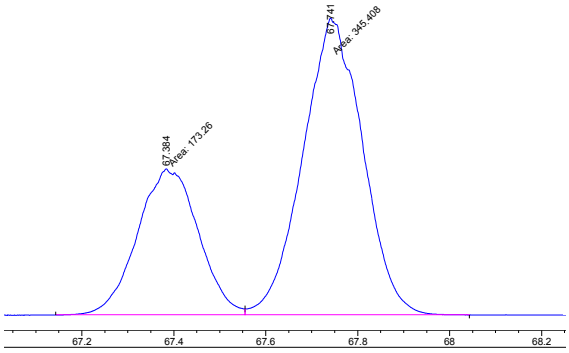
*Chiral GLC (β-dex, Supelco, 80 °C for 10 min, ramp 1 °C/min to 160 °C for 10 min, 20 psi) - analysis of title compound.*




Racemic Sample



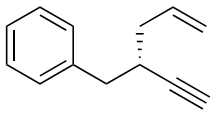

Enantioenriched Sample




co-injection of racemic and enantioenriched samples

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 67.372 | MF | 0.1552 | 106.36320 | 11.42260 | 22.62488 |
| 2 | 67.737 | FM | 0.1532 | 363.75287 | 39.56961 | 77.37512 |

**Kinetic resolution to give *(S)*-(2-ethynylpent-4-en-1-yl)benzene (Table 1.5, Entry 5):** The representative procedure was followed with 1-phenylbut-3-yn-2-yl acetate on a 0.2 mmol scale.

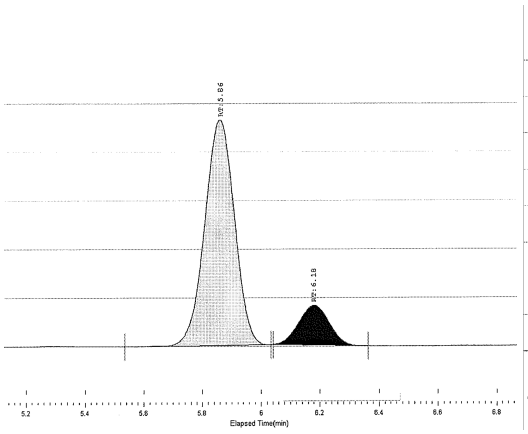


***(S)*-(2-ethynylpent-4-en-1-yl)benzene (Table 1.5, Entry 5 A)**. $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.28-7.32 (2H, m), 7.21-7.25 (3H, m), 5.92 (1H, ddddd (app dtt), *J* = 17.0 Hz, 8.5 Hz, 7.0 Hz, 7.0 Hz, 1.0 Hz), 5.12-5.13 (1H, m), 5.10 (1H, m), 2.79-2.80 (2H, m), 2.70 (1H, ddddd (app ddtd), *J* = 8.5 Hz, 8.5 Hz, 6.5 Hz, 6.5 Hz, 2.5 Hz), 2.25 (2H, m), 2.10 (1H, d, *J* = 2.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 139.2, 135.5, 129.2, 129.2, 128.2, 128.2, 126.4, 117.0, 86.6, 70.4, 40.5, 38.4, 33.3; IR (neat): 3300 (w), 3064 (m), 3028 (m), 2979 (m), 2924 (m), 2858 (w), 1641 (m), 1604 (m), 1495 (m), 1441 (m), 915 (s), 698 (s), 632 (s) $cm^{-1}$; HRMS-(ESI+) for $C_{13}H_{15}$ [M+H]: calculated: 171.1174, found: 171.1176. $[\alpha]^{22}_{D}$ = 3.2 (*c* = 0.53, $CDCl_3$). The crude reaction was purified on silica gel (pentane) to afford colorless oil. $R_f$ = 0.21 (pentane; stain in PMA).

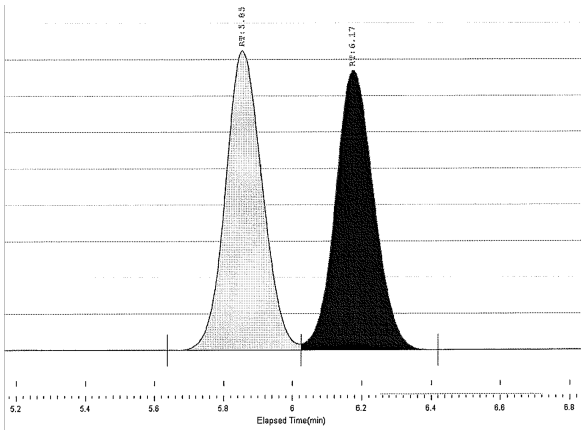
***Analysis of Stereochemistry:***

Optical purity was determined by SFC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-4-ethynylnon-1-ene (Table 1.5, Entry 1A).

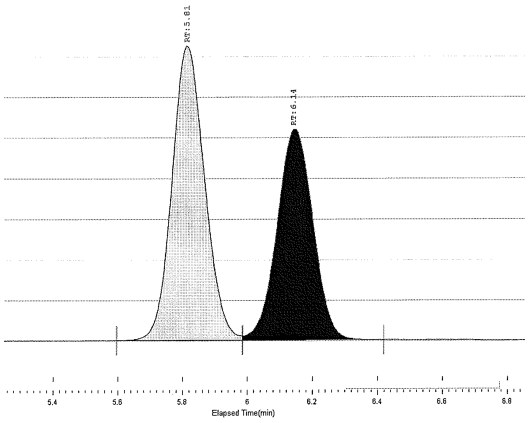
*Chiral SFC (OJ-H, Chiralpak, 215 nm, 3.0 mL/min, 1.5% i-PrOH, 100 bar, 35 °C) - analysis of title compound.*




Racemic Sample

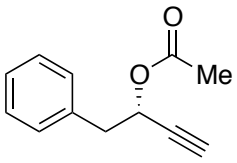



Enantioenriched Sample




co-injection of racemic and enantioenriched samples

| Peak No | % Area | Area | RT (min) |
|---|---|---|---|
| 1 | 84.6896 | 3257.8362 | 5.86 |
| 2 | 15.3104 | 588.9614 | 6.18 |
| Total: | 100 | 3846.7976 | |

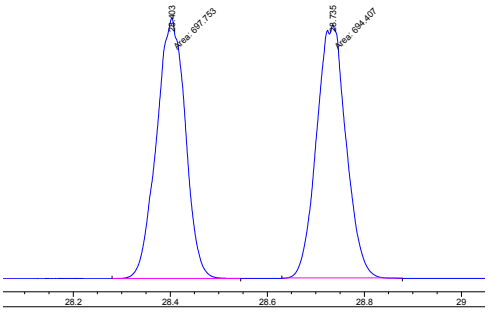


***(S)*-1-phenylbut-3-yn-2-yl acetate (Table 1.5, Entry 5B)**. The crude reaction mixture was purified on silica gel (10:1 pentane: diethyl ether) to afford a clear, colorless oil. $R_f$ = 0.7 (5:1 pentane: diethyl ether; stain in PMA). $[\alpha]^{22}_{D}$ = -7.9 (*c* = 1.33, $CDCl_3$). Spectral data is in accordance with the literature.[35]

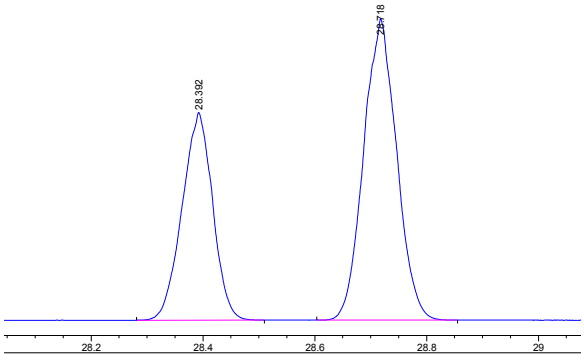
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(S)*-oct-1-yn-3-yl acetate (Table 1/5, Entry 1B).

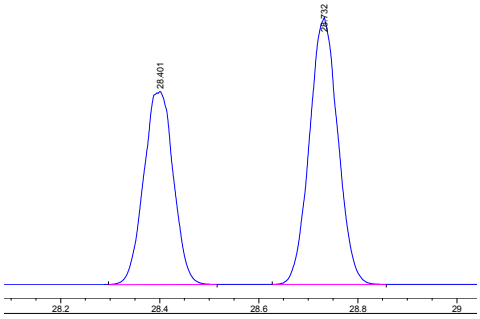
*Chiral GLC (β-dex, Supelco, 100 °C for 10 min, ramp 3 °C/min to 160 °C for 10 min, 20 psi) - analysis of title compound.*




Racemic Sample



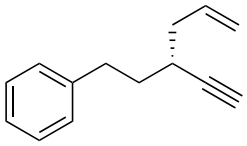

Enantioenriched Sample




| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 28.392 | BB | 0.0471 | 436.78180 | 114.99051 | 38.95276 |
| 2 | 28.718 | BB | 0.0499 | 684.52972 | 166.75691 | 61.04724 |

co-injection of racemic and enantioenriched samples

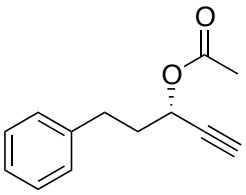
**Kinetic resolution to give *(R)*-(3-ethynylhex-5-en-1-yl)benzene (Table 1.5, Entry 6):** The representative procedure was followed with 5-phenylpent-1-yn-3-yl acetate on a 0.2 mmol scale.



***(R)*-(3-ethynylhex-5-en-1-yl)benzene (Table 1.5, Entry 6A)**. The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil. $R_f$ = 0.37 (pentane, stain in PMA). $[\alpha]^{22}_D$ = 34.6 (*c* = 0.58, $CHCl_3$). Spectral data is in accordance with the literature.[3]

***Analysis of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to *(R)*-4-ethynylnon-1-ene (Table 1.5, Entry 1A).

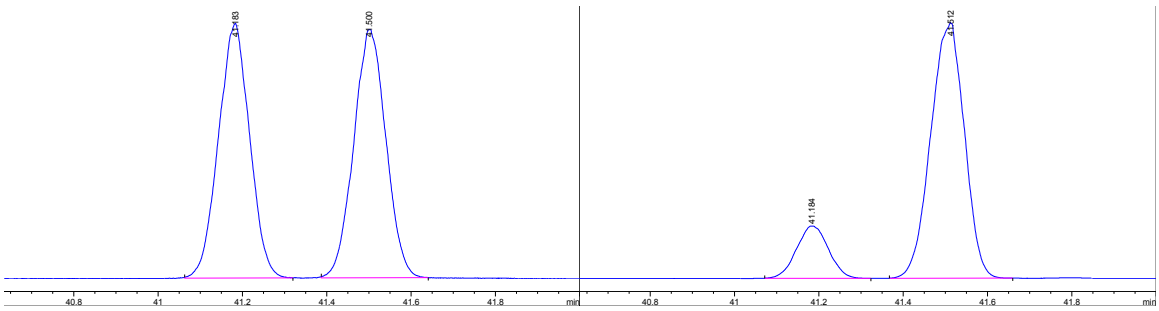


***(S)*-5-phenylpent-1-yn-3-yl acetate (Table 1.5, Entry 6B)**. The crude reaction mixture was purified on silica gel (10:1 pentane: diethyl ether) to afford a clear, colorless oil. $R_f$ = 0.21 (15:1 hexane: ethyl acetate, stain in PMA). $[\alpha]^{22}_{D}$ = -9.1 (*c* = 0.63, $CHCl_3$). Spectral data is in accordance with the literature. [2]

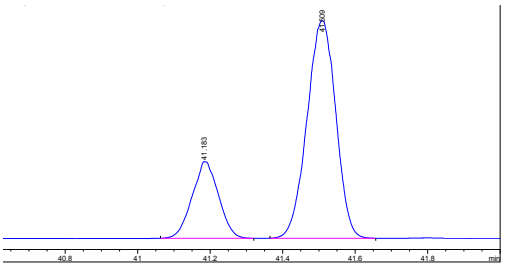
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(S)*-oct-1-yn-3-yl acetate (Table 1.5, Entry 1B).

*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 4 °C/min to 160 °C for 10 min, 20 psi) - analysis of title compound.*



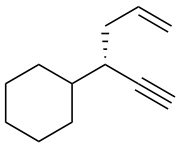

Racemic Sample Enantioenriched Sample



| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 41.184 | BB | 0.0661 | 60.81909 | 11.52059 | 16.33605 |
| 2 | 41.512 | BB | 0.0657 | 311.48068 | 56.19104 | 83.66395 |

co-injection of racemic and enantioenriched samples

K**inetic resolution to give *(S)*-hex-5-en-1-yn-3-ylcyclohexane (Table 1.5, Entry 7):** The representative procedure was followed with 1-cyclohexylprop-2-yn-1-yl acetate on a 0.2 mmol scale.

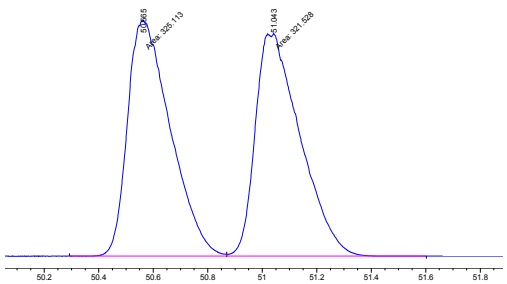


***(S)*-hex-5-en-1-yn-3-ylcyclohexane (Table 1.5, Entry 7A)**. The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil. $R_f$ = 0.64 (5:1 hexane: ethyl acetate, stain in PMA). $[\alpha]^{22}_D$ = 6.2 (*c* = 0.31, $CHCl_3$). Spectral data is in accordance with the literature. [3]

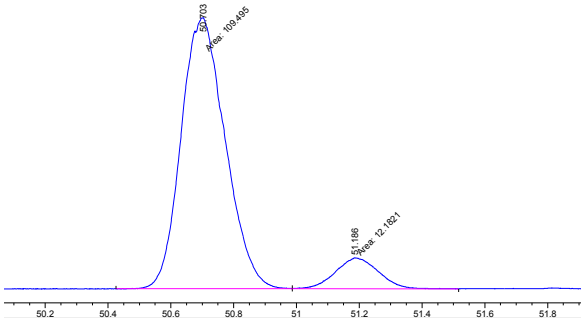
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-4-ethynylnon-1-ene (Table 1.5, Entry 1A).

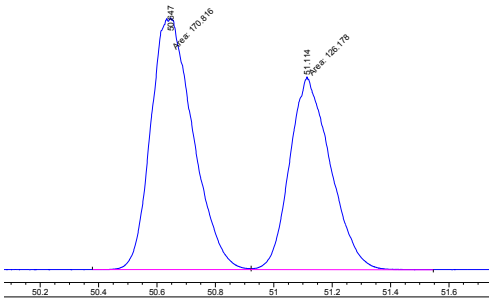
*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 1 °C/min to 140 °C for 10 min, 20 psi) - analysis of title compound.*




Racemic Sample

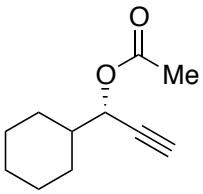



Enantioenriched Sample




co-injection of racemic and enantioenriched samples

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 50.703 | MF | 0.1627 | 109.49494 | 11.21545 | 89.98819 |
| 2 | 51.186 | FM | 0.1586 | 12.18208 | 1.28046 | 10.01181 |

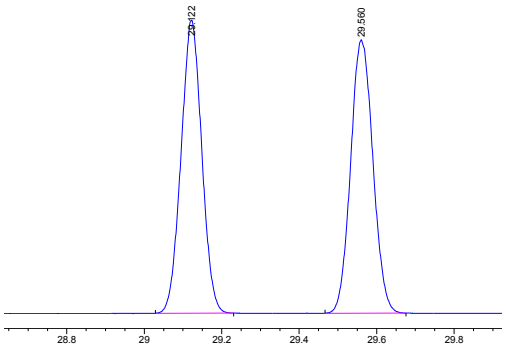



***(S)*-1-cyclohexylprop-2-yn-1-yl acetate (Table 1.5, Entry 7B)**. The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil. $R_f$ = 0.51 (pentane, stain in PMA). $[\alpha]^{22}_{D}$ = -5.0 (*c* = 1.76, $CHCl_3$). Spectral data is in accordance with the literature.[36]

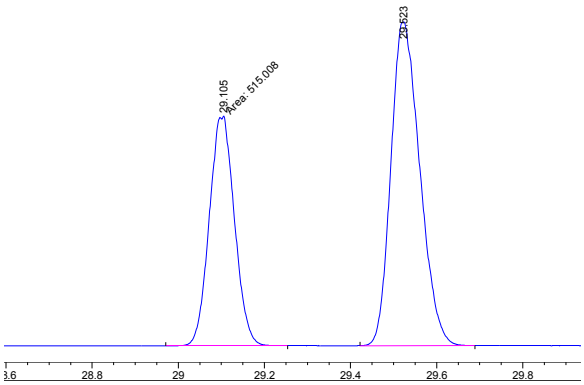
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(S)*-oct-1-yn-3-yl acetate (Table 1.5, Entry 1B).

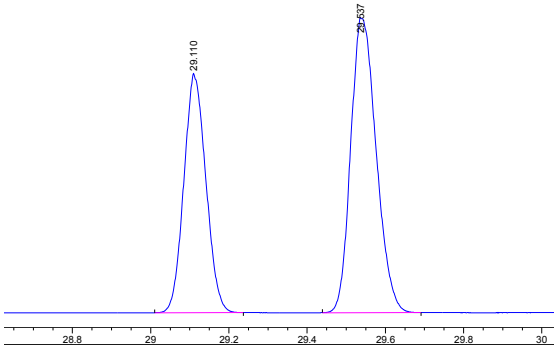
*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 5 °C/min to 140 °C for 10 min, 20 psi) - analysis of title compound.*




Racemic Sample



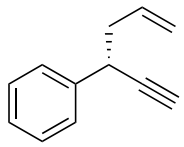

Enantioenriched Sample




co-injection of racemic and enantioenriched samples

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 29.105 | MM | 0.0675 | 515.00781 | 127.15060 | 38.15054 |
| 2 | 29.523 | BB | 0.0573 | 834.92798 | 179.27284 | 61.84946 |

**Kinetic resolution to give *(R)*-hex-5-en-1-yn-3-ylbenzene (Table 1.6, Entry 1):** The representative procedure was followed with 1-phenylprop-2-yn-1-yl acetate with the following modification: the reaction was run for 2 hours at 0.5% catalyst loading on a 0.2 mmol scale.



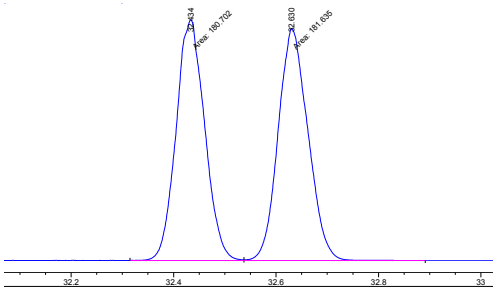
***(R)*-hex-5-en-1-yn-3-ylbenzene (Table 1.6, Entry 1 A)**. The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil. $R_f$ = 0.43 (pentane, stain in PMA). $[\alpha]^{22}_D$ = -15.2 (*c* = 0.31, $CHCl_3$). Spectral data is in accordance with the literature.[39]

***Analysis of Stereochemistry:***

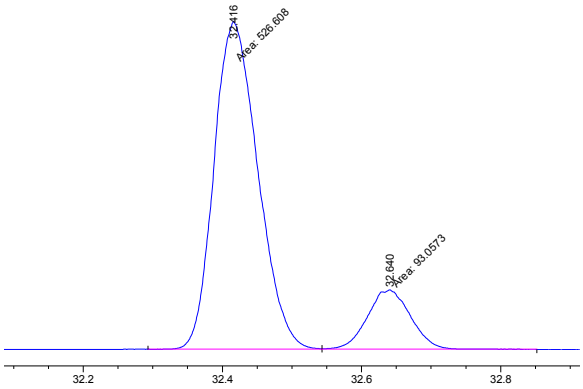
Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned as shown below.

*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 3 °C/min to 140 °C for 10 min, 20 psi) - analysis of title compound.*

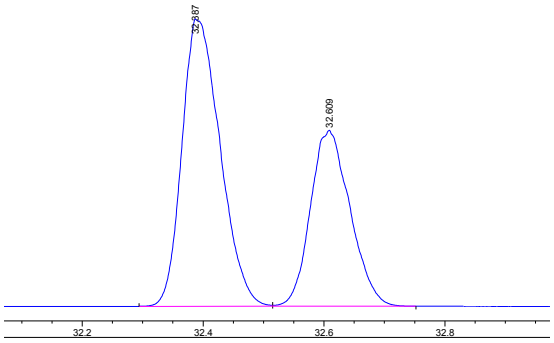
[39] Zhan, Z.; Yo, J.; Liu, H.; Cui, Y.; Yang, R.; Yang, W.; Li, Y. *J. Org. Chem.* **2006**, *71*, 8298.




Racemic Sample




Enantioenriched Sample

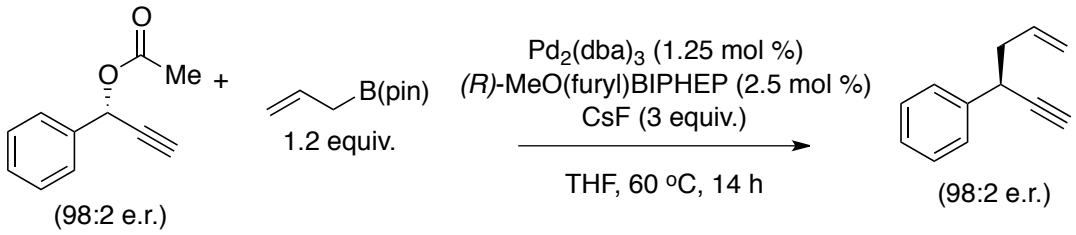



| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 32.416 | MF | 0.0727 | 526.60809 | 120.75000 | 84.98265 |
| 2 | 32.640 | FM | 0.0711 | 93.05730 | 21.80412 | 15.01735 |

co-injection of racemic and enantioenriched samples

***Proof of Absolute Stereochemistry:***

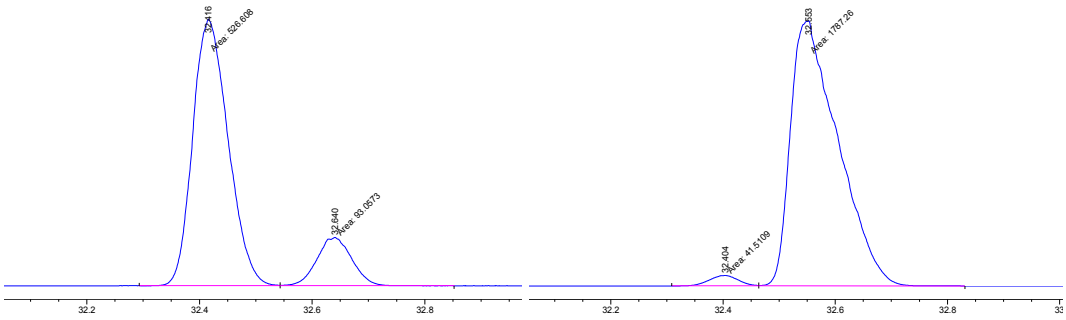
In order to determine the absolute stereochemistry, the title compound was compared by GLC analysis to authentic *(S)*-hex-5-en-1-yn-3-ylbenzene, prepared by the stereospecific enyne cross coupling as depicted below.[3]



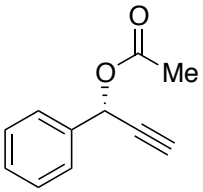

(98:2 e.r.)

(98:2 e.r.)

*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 3 °C/min to 140 °C for 10 min, 20 psi)-analysis of title compound.*




*Title Compound* authentic *(S)*-hex-5-en-1-yn-3-ylbenzene

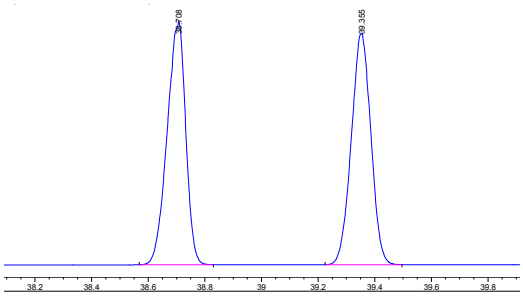



***(R)*-1-phenylprop-2-yn-1-yl acetate (Table 1.6, Entry 1B)**. The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil. $R_f$ = 0.27 (25:1 hexane: ethyl acetate, stain in PMA). $[\alpha]^{22}_D$ = 2.2 (*c* = 0.45, $CHCl_3$). Spectral data is in accordance with the literature.[36]

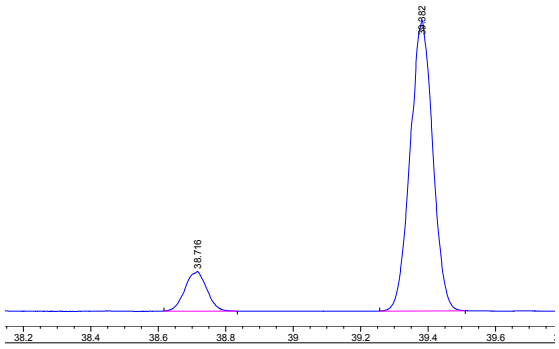
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned as shown below.

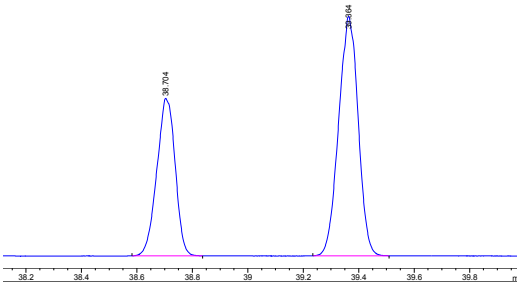
*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 3 °C/min to 140 °C for 20 min, 20 psi) - analysis of title compound.*




Racemic Sample




Enantioenriched Sample

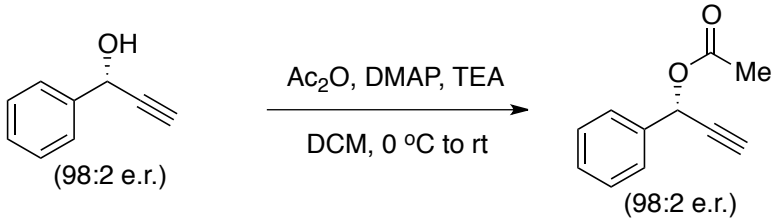



co-injection of racemic and enantioenriched samples

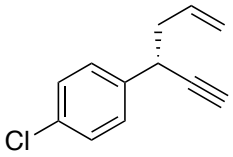
| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 38.716 | BB | 0.0548 | 19.52114 | 4.33718 | 11.65692 |
| 2 | 39.382 | BB | 0.0573 | 147.94279 | 31.80352 | 88.34308 |

***Proof of Absolute Stereochemistry:***

In order to determine the absolute stereochemistry, the optical rotation of the title compound [$[\alpha]^{22}_{D}$ = 2.2 (*c* = 0.45, $CHCl_3$), 88:11 e.r.] was compared to authentic *(R)*-1-phenylprop-2-yn-1-yl acetate prepared from commercially available *(R)*-1-phenylprop-2-yn-1-ol as shown below [$[\alpha]^{22}_{D}$ = 4.8 (*c* = 0.915, $CHCl_3$), 98:2 e.r.]




**Kinetic resolution to give *(R)*-1-chloro-4-(hex-5-en-1-yn-3-yl)benzene (Table 1.6, Entry 2):** The representative procedure was followed with 1-(4-chlorophenyl)prop-2-yn-1-yl acetate with the following modification: the reaction was run for 2 hours at 0.5% catalyst loading on a 0.2 mmol scale.

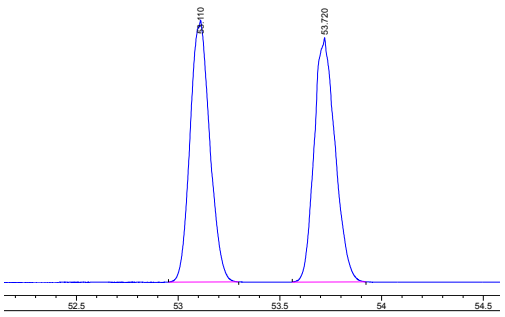



***(R)*-1-chloro-4-(hex-5-en-1-yn-3-yl)benzene (Table 1.6, Entry 2A)**. The crude reaction mixture was purified on silica gel (pentane) to afford a clear, colorless oil. $R_f$ = 0.37 (pentane, stain in PMA). $[\alpha]^{22}_D$ = -5.6 (*c* = 0.60, $CHCl_3$). Spectral data is in accordance with the literature. [37]

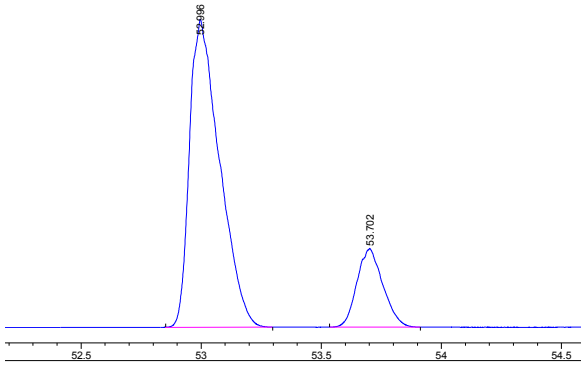
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-hex-5-en-1-yn-3-ylbenzene (Table 1.6, Entry 1A).

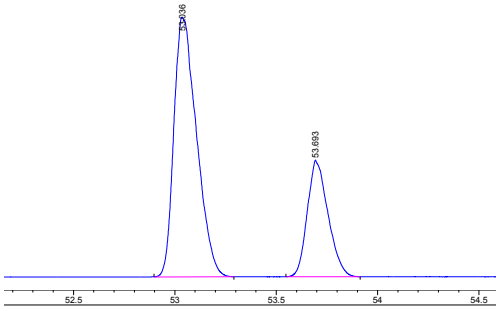
*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 2 °C/min to 140 °C for 10 min, 20 psi) - analysis of title compound.*




Racemic Sample

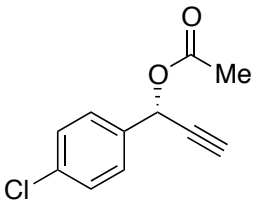



Enantioenriched Sample




co-injection of racemic and enantioenriched samples

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 52.996 | BB | 0.1041 | 1385.26355 | 159.45381 | 81.93271 |
| 2 | 53.702 | BB | 0.0887 | 305.46964 | 40.77204 | 18.06729 |

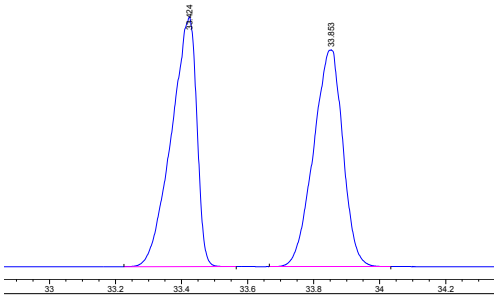



***(R)*-1-(4-chlorophenyl)prop-2-yn-1-yl acetate (Table 1.6, Entry 12 B)**. The crude reaction mixture was purified on silica gel (10:1 pentane:diethyl ether) to afford a clear, colorless oil. $R_f$ = 0.32 (10:1 hexane: ethyl acetate, stain in PMA). $[\alpha]^{22}_{D}$ = 9.8 (*c* = 1.22, $CHCl_3$). Spectral data is in accordance with the literature.[34]

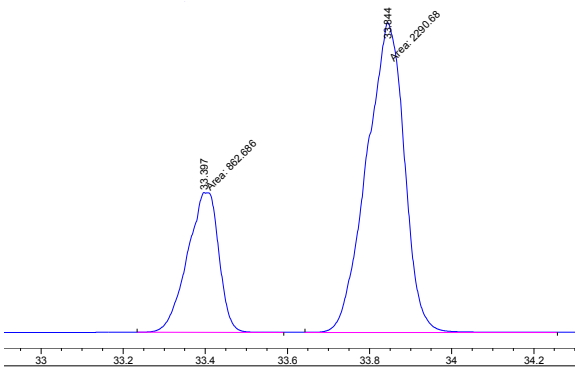
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-1-phenylprop-2-yn-1-yl acetate (Table 1.6, Entry 1B).

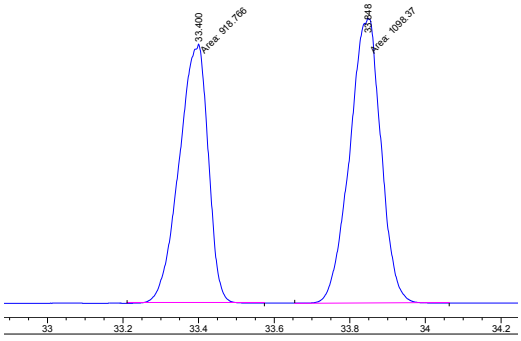
*Chiral GLC (β-dex, Supelco, 100 °C for 10 min, ramp 3 °C/min to 160 °C for 10 min, 20 psi) - analysis of title compound.*




Racemic Sample




Enantioenriched Sample

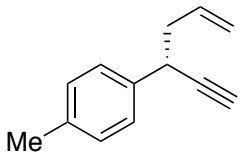



co-injection of racemic and enantioenriched samples

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 33.397 | MM | 0.0885 | 862.68561 | 162.41209 | 27.35757 |
| 2 | 33.844 | MM | 0.1061 | 2290.68481 | 359.74545 | 72.64243 |

**Kinetic resolution to give *(R)*-1-(hex-5-en-1-yn-3-yl)-4-methylbenzene (Table 1.6, Entry**

**3):** The representative procedure was followed with 1-(p-tolyl)prop-2-yn-1-yl acetate with the following modification: the reaction was run for 2 hours at 0.5% catalyst loading on a 0.2 mmol scale.



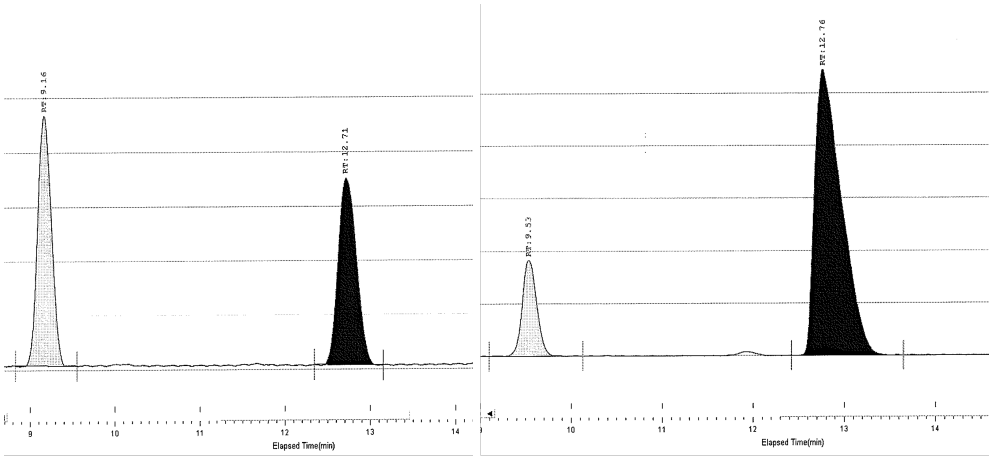

***(R)*-1-(hex-5-en-1-yn-3-yl)-4-methylbenzene (Table 1.6, Entry 3A)**. $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.25 (2H, ddd, *J* = 8.0 Hz, 2.0 Hz, 2.0 Hz), 7.14 (2H, d, *J* = 8.0 Hz), 5.85 (1H, dddd (app ddt), *J* = 17.0 Hz, 10.0 Hz, 6.5 Hz, 6.5 Hz), 5.09 (1H, ddd, *J* = 1.5 Hz, 1.5 Hz, 1.5 Hz), 5.04 - 5.07 (1H, m), 3.69 (1H, ddd (app dt), *J* = 7.0 Hz, 7.0 Hz, 2.5 Hz), 2.50 (2H, dddd (app ddt), *J* = 6.5 Hz, 6.5 Hz, 2.5 Hz, 1.5 Hz), 2.33 (3H, s), 2.28 (1H, d, *J* = 2.5); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 137.8, 136.5, 135.3, 129.2, 129.2, 127.3, 127.3, 117.1, 85.6, 71.2, 42.4, 37.3, 21.1; IR (neat): 3299 (w), 3051(m), 3007 (m), 2923 (w), 2857 (m), 1513 (m), 1022 (m), 915 (m), 813 (m), 634 (s) $cm^{-1}$; HRMS-(ESI+) for $C_{13}H_{15}$ [M+H]: calculated: 171.1174, found: 171.1179. $[\alpha]^{22}_{D}$ = -60.0 (*c* = 0.05, $CHCl_3$). The crude reaction was purified on silica gel (pentane) to afford a clear, colorless oil. $R_f$ = 0.23 (pentane; stain in PMA).

***Analysis of Stereochemistry:***

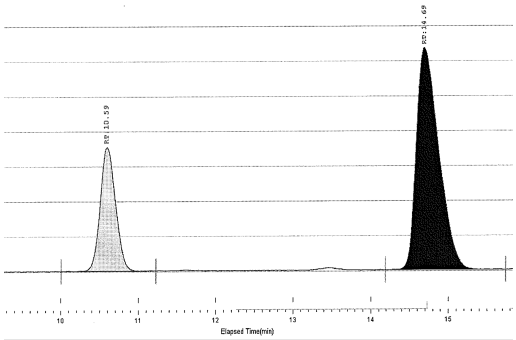
Optical purity was determined by SFC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-hex-5-en-1-yn-3-ylbenzene (Table 1.6, Entry 1A).

*Chiral SFC (OJ-H, Chiralpak, 215 nm, 3.0 mL/min, 1% 1:1 i-PrOH:Hexanes, 100 bar, 35 °C)*

*- analysis of title compound.*

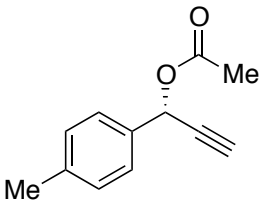



Racemic Sample Enantioenriched Sample




| Peak No | % Area | Area | RT (min) |
|---|---|---|---|
| 1 | 15.3555 | 4031.9559 | 9.53 |
| 2 | 84.6445 | 22225.3857 | 12.76 |
| Total: | 100 | 26257.3416 | |

co-injection of racemic and enantioenriched samples

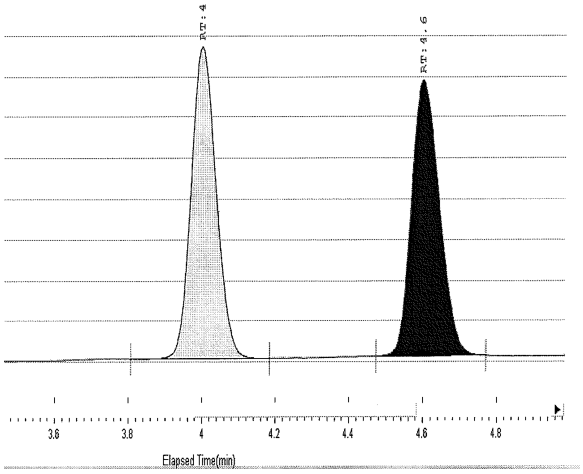



***(R)*-1-(p-tolyl)prop-2-yn-1-yl acetate (Table 1.6, Entry 3B)**. The crude reaction mixture was purified on silica gel (10:1 pentane: diethyl ether) to afford a clear, colorless oil. $R_f$ = 0.26 (25:1 hexane: ethyl acetate; stain in PMA). $[\alpha]^{22}_{D}$ = 26.177 (*c* = 0.11, $CHCl_3$). Spectral data is in accordance with the literature. [1]

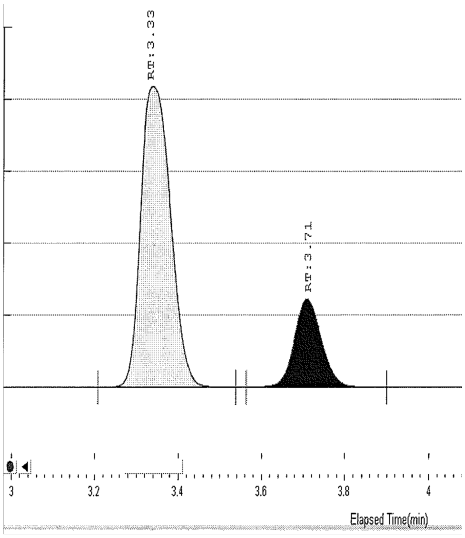
***Analysis of Stereochemistry:***

Optical purity was determined by SFC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-1-phenylprop-2-yn-1-yl acetate (Table 1.6, Entry 1B).

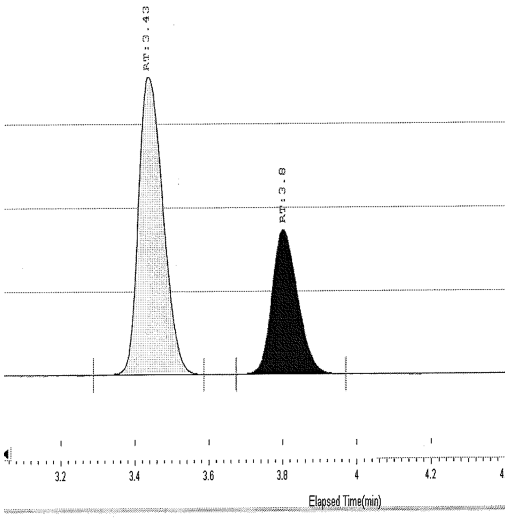
*Chiral SFC (OJ-H, Chiralpak, 215 nm, 3.0 mL/min, 3% i-PrOH, 100 bar, 35 °C) - analysis of title compound.*




Racemic Sample



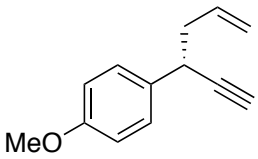

Enantioenriched Sample




| Peak No | % Area | Area | RT (min) |
|---|---|---|---|
| 1 | 78.8757 | 10298.8407 | 3.33 |
| 2 | 21.1243 | 2758.2045 | 3.71 |
| Total: | 100 | 13057.0452 | |

co-injection of racemic and enantioenriched samples

**Kinetic resolution to give *(R)*-1-(hex-5-en-1-yn-3-yl)-4-methoxybenzene (Table 1.6, Entry 1A):** The representative procedure was followed with 1-(4-methoxyphenyl)prop-2-yn-1-yl acetate with the following modification: the reaction was run for 1 hour at 0.5% catalyst loading on a 0.2 mmol scale.

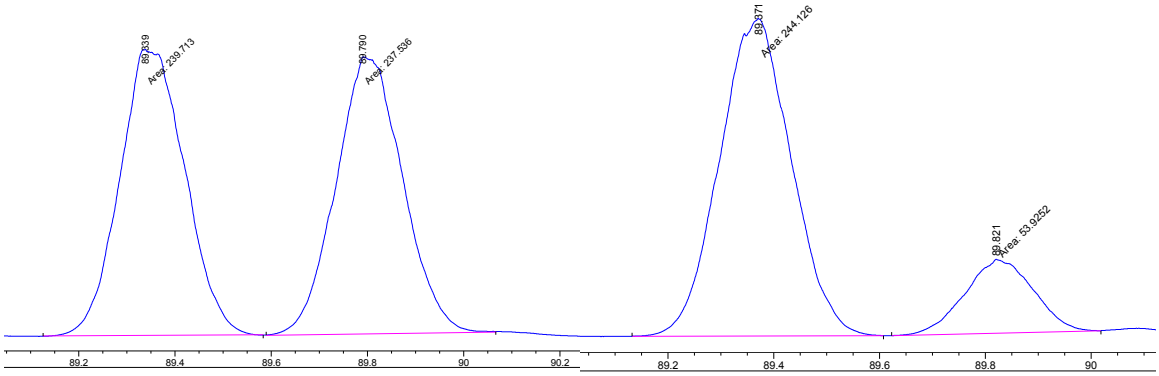



***(R)*-1-(hex-5-en-1-yn-3-yl)-4-methoxybenzene (Table 1.6, Entry 2A)**. The crude reaction mixture was purified on silica gel (10:1 pentane: diethyl ether) to afford a clear, colorless oil. $R_f$ = 0.86 (10:1 pentane: diethyl ether, stain in $KMNO_4$). $[\alpha]^{22}_D$ = 13.9 (c = 0.73, $CHCl_3$). Spectral data is in accordance with the literature.[37]

***Analysis of Stereochemistry:***

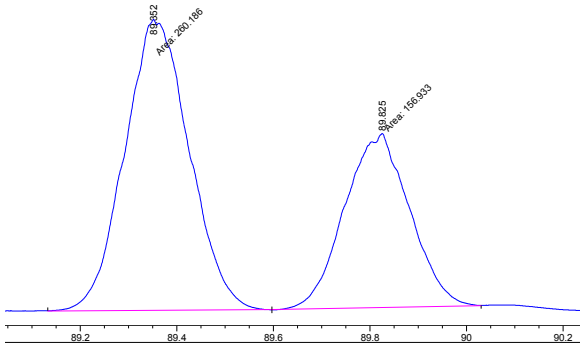
Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-hex-5-en-1-yn-3-ylbenzene (Table 1.6, Entry 1A).

*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 1 °C/min to 160 °C for 20 min, 20 psi) - analysis of title compound.*



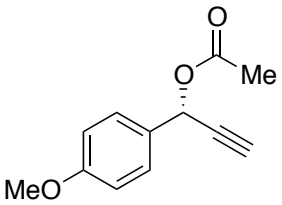

Racemic Sample

Enantioenriched Sample




| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 89.371 | MM | 0.1571 | 244.12610 | 25.89414 | 81.90742 |
| 2 | 89.821 | MM | 0.1491 | 53.92517 | 6.02781 | 18.09258 |

co-injection of racemic and enantioenriched samples

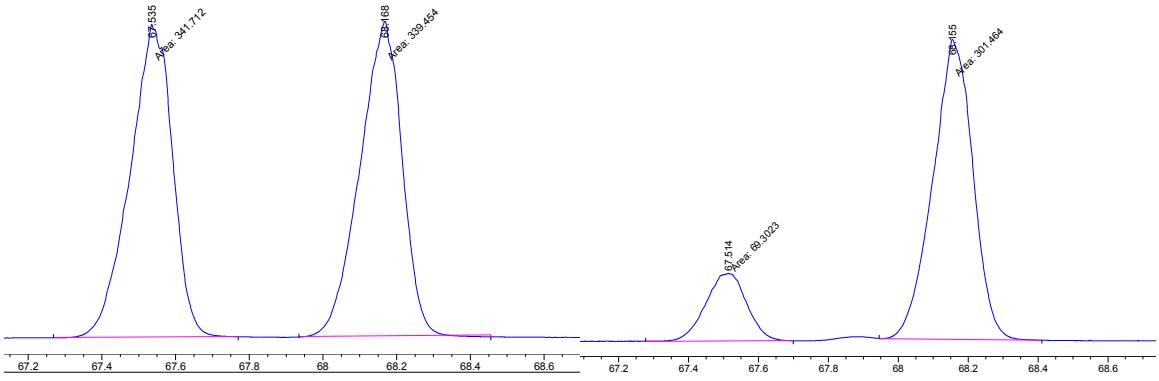


***(R)*-1-(4-methoxyphenyl)prop-2-yn-1-yl acetate (Table 1.6, Entry 4B)**. The crude reaction mixture was purified on silica gel (10:1 pentane: diethyl ether) to afford a clear, colorless oil. $R_f$ = 0.39 (10:1 pentane: diethyl ether, stain in $KMNO_4$). $[\alpha]^{22}_D$ = 20.3 (c = 0.92, $CHCl_3$). Spectral data is in accordance with the literature. [37]

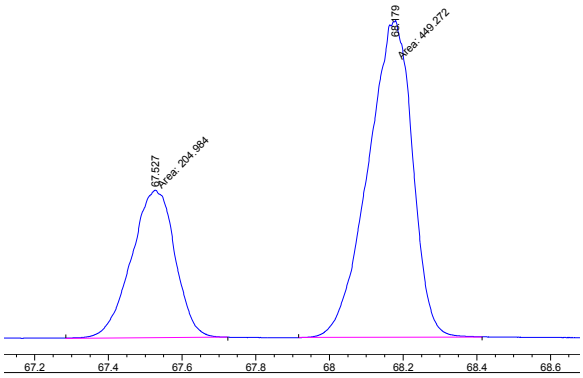
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-1-phenylprop-2-yn-1-yl acetate (Table 1.6, Entry 1B).

*Chiral GLC (β-dex, Supelco, 40 °C for 10 min, ramp 2.5 °C/min to 160 °C for 20 min, 20 psi) - analysis of title compound.*



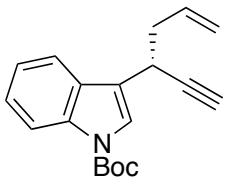

Racemic Sample Enantioenriched Sample




| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 67.514 | MM | 0.1357 | 69.30232 | 8.51125 | 18.69166 |
| 2 | 68.155 | MM | 0.1332 | 301.46375 | 37.73237 | 81.30834 |

co-injection of racemic and enantioenriched samples

**Kinetic resolution to give *(R)*-tert-butyl 3-(hex-5-en-1-yn-3-yl)-1H-indole-1-carboxylate (Table 1.6, Entry 5):** The representative procedure was followed with tert-butyl 3-(1-acetoxyprop-2-yn-1-yl)-1H-indole-1-carboxylate with the following modification: the reaction was run for 1 hour at 0.5% catalyst loading on a 0.2 mmol scale.



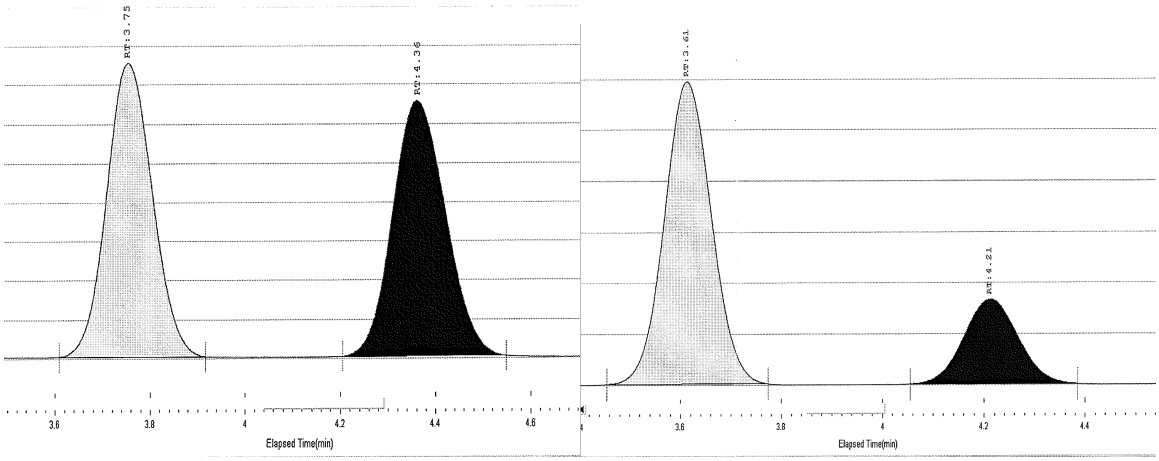

***(R)*-tert-butyl 3-(hex-5-en-1-yn-3-yl)-1H-indole-1-carboxylate (Table 1.6, Entry 5A)**. The crude reaction mixture was purified on silica gel (10:1 pentane:diethyl either) to afford a clear, colorless oil. $R_f$ = 0.93 (10:1 pentane:diethyl ether, stain in $KMNO_4$). $[\alpha]^{22}_D$ = -4.1 (c = 0.73, $CHCl_3$). Spectral data is in accordance with the literature. [37]

***Analysis of Stereochemistry:***

Optical purity was determined by SFC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-hex-5-en-1-yn-3-ylbenzene (Table 1.6, Entry 2A).

*Chiral SFC (OJ-H, Chiralpak, 215 nm, 3.0 mL/min, 1% 1:1 i-PrOH:Hexanes, 100 bar, 35 °C)*

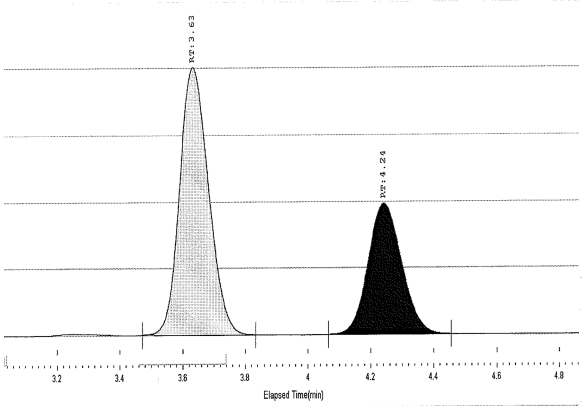
*- analysis of title compound.*




Racemic Sample

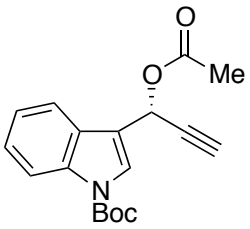



Enantioenriched Sample




| Peak Info | | | | |
|---|---|---|---|---|
| **Peak Name** | **Number** | | **Concentration** | **Area %** |
| Peak1 | 1 | | 0 | 75.6151 |
| Peak2 | 2 | | 0 | 24.3849 |
| **RT (min)** | | **St. (min)** | **End (min)** | **Height** |
| 3.61 | | 3.4547 | 3.7714 | 1187.8859 |
| 4.21 | | 4.0547 | 4.383 | 332.7256 |

co-injection of racemic and enantioenriched samples

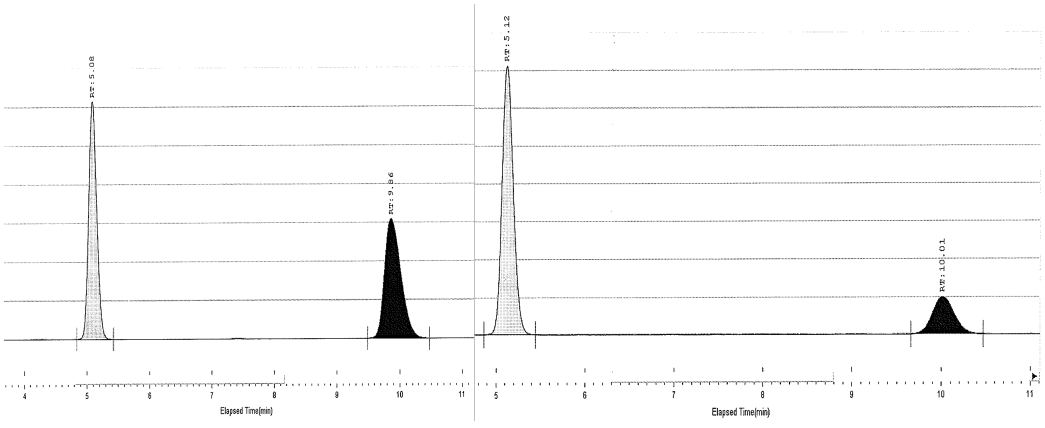



***(R)-tert*-butyl 3-(1-acetoxyprop-2-yn-1-yl)-1H-indole-1-carboxylate (Table 1.6, Entry 5B)**. The crude reaction mixture was purified on silica gel (10:1 pentane:diethyl either) to afford a clear, colorless oil. $R_f$ = 0.35 (10:1 pentane:diethyl either, stain in $KMnO_4$). $[\alpha]^{22}_D$ = -2.4 (c = 1.15, $CHCl_3$). Spectral data is in accordance with the literature. [37]

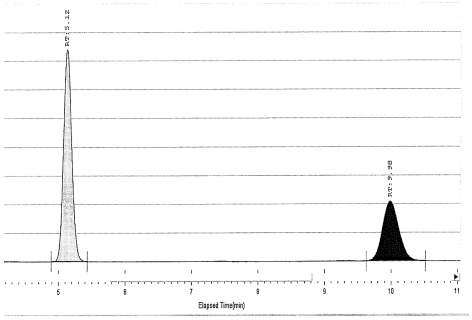
***Analysis of Stereochemistry:***

Optical purity was determined by SFC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-1-phenylprop-2-yn-1-yl acetate (Table 1.6, Entry 2B).

*Chiral SFC (OJ-H, Chiralpak, 215 nm, 3.0 mL/min, 1% 1:1 i-PrOH:Hexanes, 100 bar, 35 °C) - analysis of title compound.*



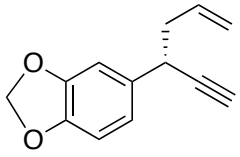

Racemic Sample Enantioenriched Sample



| Peak Info | | | |
|---|---|---|---|
| Peak No | % Area | Area | RT (min) |
| 1 | 79.0279 | 6306.2126 | 5.12 |
| 2 | 20.9721 | 1673.5195 | 10.01 |
| Total: | 100 | 7979.7321 | |

co-injection of racemic and enantioenriched samples

**Kinetic resolution to give *(R)*-5-(hex-5-en-1-yn-3-yl)benzo[d][1,3]dioxole (Table 1.6, Entry 6):** The representative procedure was followed with 1-(benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-yl acetate with the following modification: the reaction was run for 2 hours at 0.5% catalyst loading on a 0.2 mmol scale.



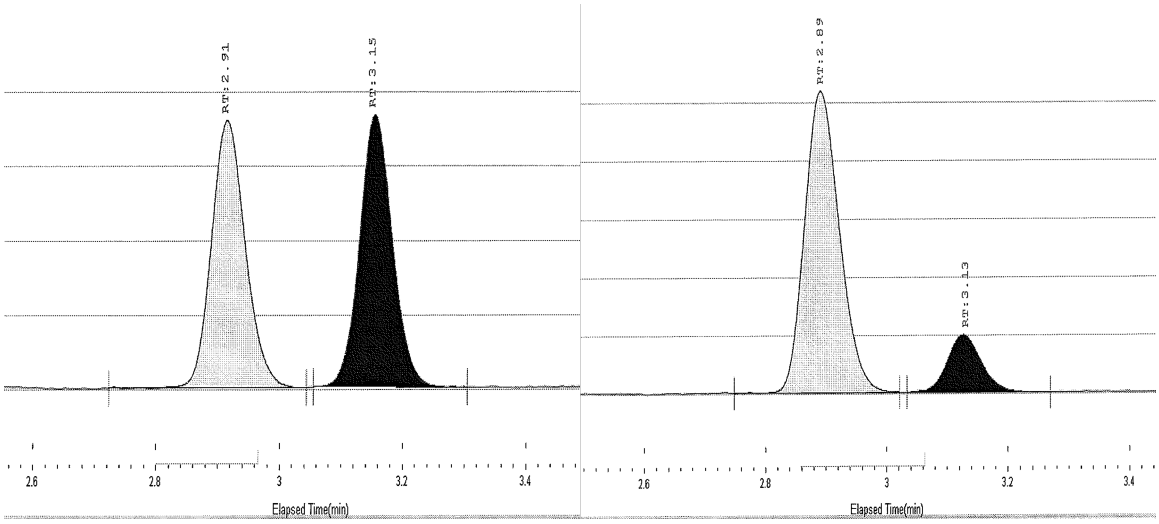
***(R)*-5-(hex-5-en-1-yn-3-yl)benzo[d][1,3]dioxole (Table 1.6, Entry 6A)**. $^{1}$H NMR (500 MHz, $CDCl_3$): δ 6.87 (1H, d, *J* = 2.0 Hz), 6.80 (1H, dd, *J* = 8.0 Hz, 2.0 Hz), 6.75 (1H, d, *J* = 8.0 Hz), 5.94 (2H, dd, *J* = 2.0 Hz, 2.0 Hz), 5.83 (1H, dddd (app ddt), *J* = 17.0 Hz, 10.5 Hz, 7.0 Hz, 7.0 Hz), 5.07-5.09 (1H, m), 5.04-5.06 (1H, m), 3.32 (1H, ddd (app dt), *J* =7.0 Hz, 7.0 Hz, 2.5 Hz), 2.46-4.50 (2H, m), 2.94 (1H, d, *J* = 2.5 Hz) ; $^{13}$C NMR (125 MHz, $CDCl_3$): δ 147.7, 146.4, 135.0, 134.6, 120.5, 117.2, 108.1, 107.9, 101.0, 85.4, 71.3, 42.5, 37.4; IR (neat): 3293 (m), 3077 (w), 2979 (w), 2895 (m), 1485 (m), 2439 (s), 1245 (s), 918 (m), 634 (s) $cm^{-1}$; HRMS-(ESI+) for $C_{13}H_{13}O_2$ [M+H]: calculated: 200.0837, found: 200.0837. $[\alpha]^{22}_{D}$ = 28.3 (*c* = 0.37, $CHCl_3$). The crude reaction was purified on silica gel (60:1 pentane:diethyl ether) to afford a clear, colorless

oil. $R_f$ = 0.10 (pentane; stain in PMA).

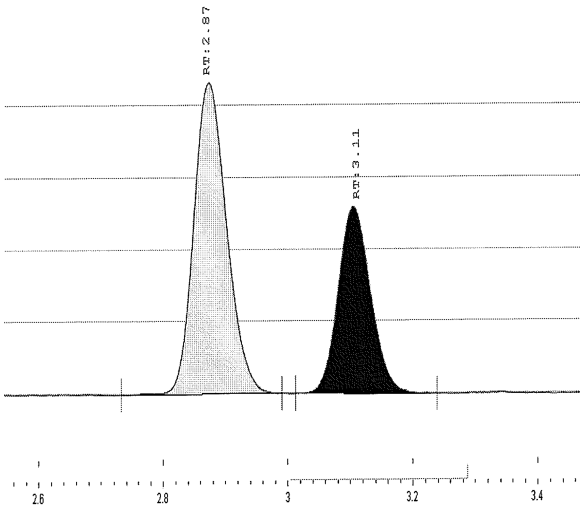
***Analysis of Stereochemistry:***

Optical purity was determined by SFC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-hex-5-en-1-yn-3-ylbenzene (Table 1.6, Entry 1A).

*Chiral SFC (AD-H, Chiralpak, 215 nm, 3.0 mL/min, 3% i-PrOH, 100 bar, 35 °C) - analysis of title compound.*

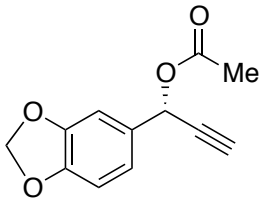



Racemic Sample Enantioenriched Sample




| Peak Info | | | |
|---|---|---|---|
| Peak No | % Area | Area | RT (min) |
| 1 | 84.386 | 1026.7635 | 2.89 |
| 2 | 15.614 | 189.9822 | 3.13 |
| Total: | 100 | 1216.7457 | |

co-injection of racemic and enantioenriched samples

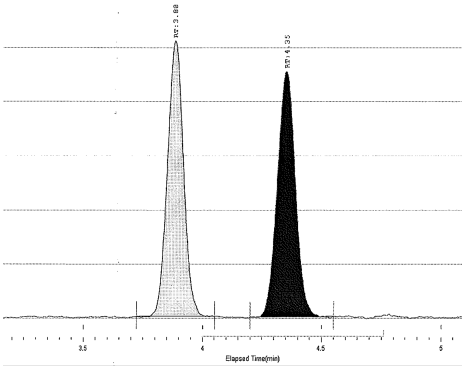



***(R)*-1-(benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-yl acetate (Table 1.6, Entry 6B)**. The crude reaction was purified on silica gel (10:1 pentane:diethyl ether) to afford a white solid. $R_f$ = 0.14 (20:1 hexane: ethyl acetate; stain in PMA). $[\alpha]^{22}_D$ = 3.7 (*c* = 0.38, $CHCl_3$). Spectral data is in accordance with the literature. [38]

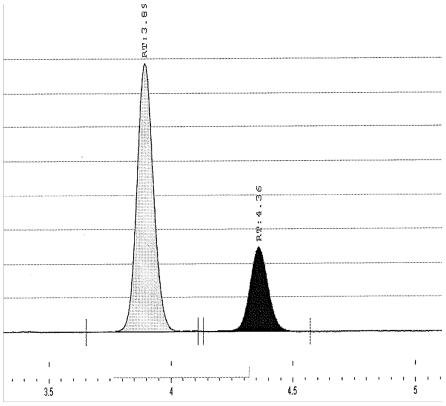
***Analysis of Stereochemistry:***

Optical purity was determined by SFC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-1-phenylprop-2-yn-1-yl acetate (Table 1.6, Entry 1B).

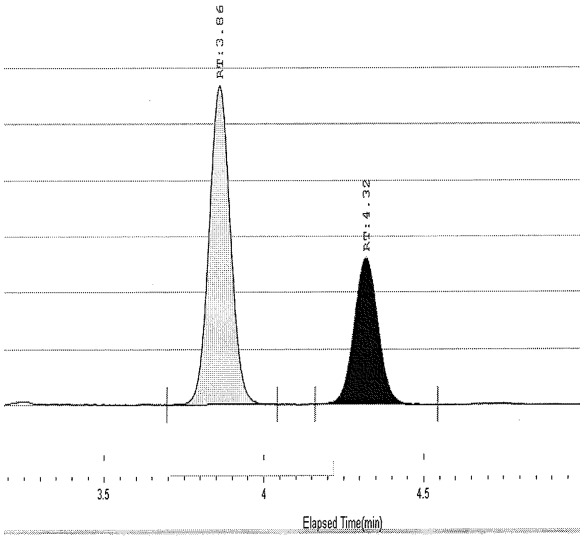
*Chiral SFC (OJ-H, Chiralpak, 215 nm, 3.0 mL/min, 3% i-PrOH, 100 bar, 35 °C) - analysis of title compound.*




Racemic Sample



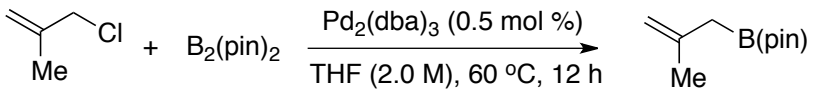

Enantioenriched Sample




co-injection of racemic and enantioenriched samples

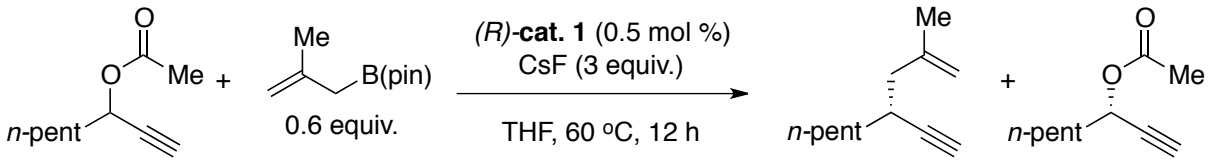
| Peak Info | | | |
|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** |
| 1 | 74.5721 | 1853.3292 | 3.89 |
| 2 | 25.4279 | 631.9564 | 4.36 |
| Total: | 100 | 2485.2856 | |

**Preparation of 2-Methallylboronic acid Pinacol Ester**



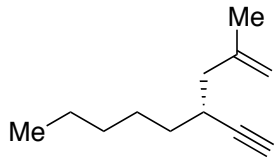

An oven-dried scintillation vial equipped with a magnetic stir bar was charged with $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol), bis(pinacolato)diboron (762.6 mg, 3.00 mmol), and tetrahydrofuran (1.5 mL) in a dry-box under argon atmosphere. The vial was capped and stirred for two minutes, then 3-chloro-2-methylpropane (271.7 mg, 3.00 mmol) was added. The vial was capped with a teflon cone-lined cap, sealed with electrical tape, removed from the dry-box, and heated to 60 °C and allowed to stir for 12 h. The reaction was then concentrated *in vacuo* and the crude reaction mixture was purified rapidly on oven-dried silica gel (50:1 pentane:diethyl ether) to afford a clear, colorless oil (341 mg, 63% yield). $R_f$ = 0.63 (50:1 pentane:diethyl ether, stain in $KMnO_4$). Spectral data is in accordance with the literature.[40]

**Kinetic Resolution to Give *(R)*-4-ethynyl-2-methylnon-1-ene (Scheme 1.17, eq 1):**




[40] Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686.

An oven-dried scintillation vial equipped with a magnetic stir bar was charged successively with [*(R)*-(+)-2,2'-Bis(di-2-furanylphosphino)-6,6'-dimethoxy-1,1'-biphenyl]palladium(II) dichloride (0.72 mg, 1.0 µmol), THF (0.4 mL), oct-1-yn-3-yl acetate (33.6 mg, 0.20 mmol), 2-methallylboronic acid pinacol ester (21.8 mg, 0.12 mmol), and cesium fluoride (91.9 mg, 0.6 mmol) in a dry-box under argon atmosphere. The vial was sealed, removed from the dry-box, and heated to 60 °C while allowing to stir for 12 h. After this time, the reaction mixture was diluted with diethyl ether, filtered through a plug of silica gel and concentrated *in vacuo*.

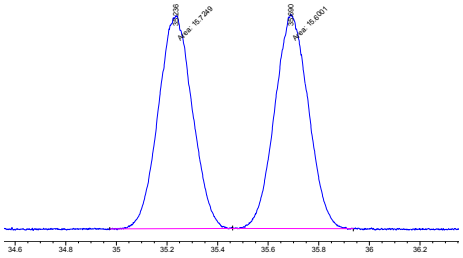



***(R)*-4-ethynyl-2-methylnon-1-ene**: The crude reaction mixture was purified on silica gel (20:1 pentane:diethyl ether) to afford a clear, colorless oil. $R_f$ = 0.95 (20:1 pentane:diethyl ether, stain in $KMNO_4$). Spectral data is in accordance with the literature. [37]

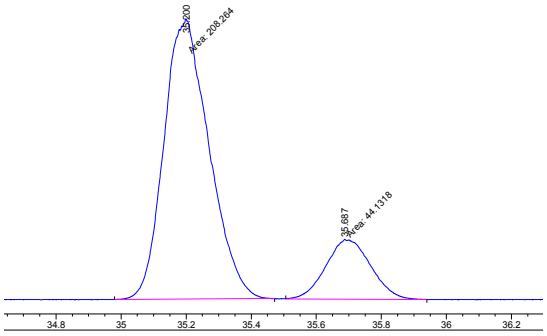
***Analysis of Stereochemistry:***

Optical purity was determined by GLC analysis of the title compound as compared to racemic product. The absolute stereochemistry was assigned by analogy to *(R)*-4-ethynylnon-1-ene (Table 1.5, Entry 1A). **Note:** The enantiomer ratios values presented in the report are an average of two runs.

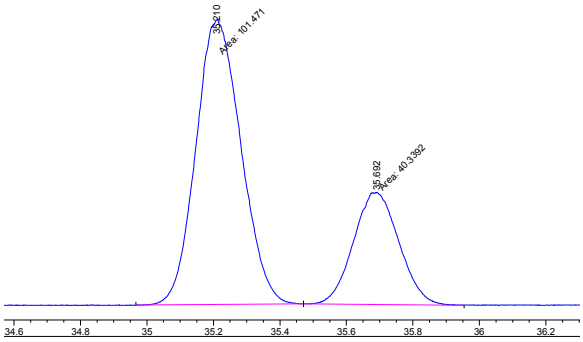
*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 1 °C/min to 140 °C for 10 min, 20 psi) - analysis of title compound.*



Racemic Sample



Enantioenriched Sample

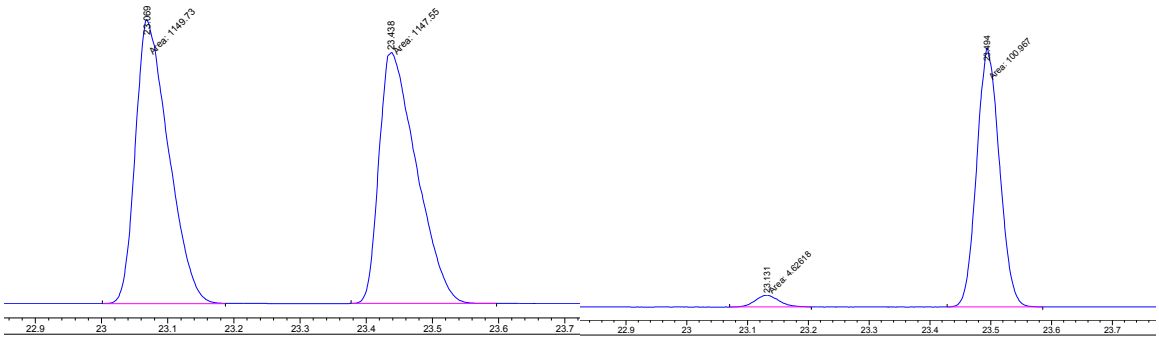


co-injection of racemic and enantioenriched samples

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 35.200 | MM | 0.1606 | 208.26378 | 21.60966 | 82.51483 |
| 2 | 35.687 | MM | 0.1594 | 44.13179 | 4.61521 | 17.48517 |

**Recovered *(S)*-oct-1-yn-3-yl acetate:**

*Chiral GLC (β-dex, Supelco, 60 °C for 10 min, ramp 1 °C/min to 140 °C for 10 min, 20 psi) - analysis of title compound.*

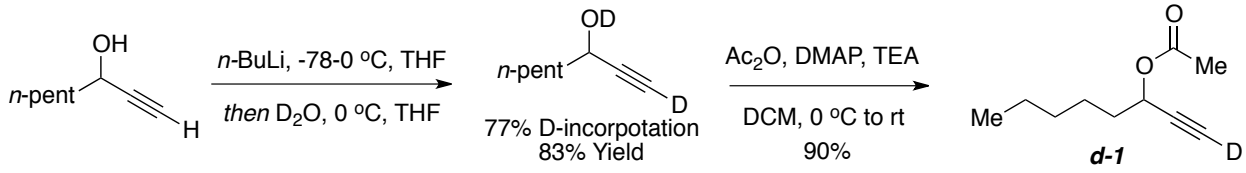



Racemic Sample Enantioenriched Sample

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 23.131 | MM | 0.0441 | 4.62618 | 1.74884 | 4.38112 |
| 2 | 23.494 | MM | 0.0435 | 100.96746 | 38.71632 | 95.61888 |

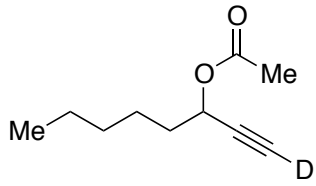
*1.6.3 Kinetic Isotope Effect Studies*

The kinetic isotope effect was measured experimentally through a competition experiment between authentic oct-1-yn-3-yl acetate and its deuterated analogue, prepared from commercially available oct-1-yn-3-ol via the two step procedure as shown below:




A flame-dried round-bottomed flask with a magnetic stir bar was charged with THF

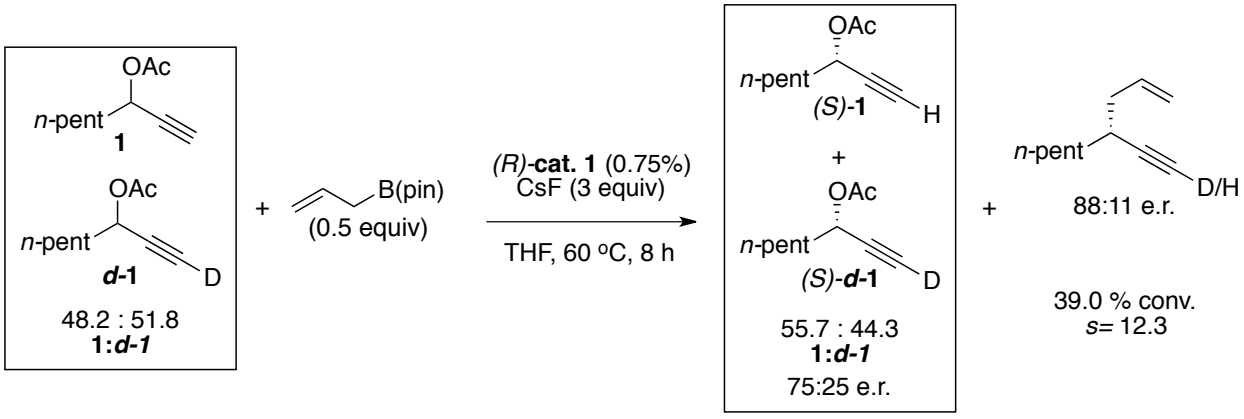
(50 mL) and oct-1-yn-3-ol (631 mg, 5.0 mmol) under nitrogen, and the solution was stirred and cooled to −78 °C. *n*-Butyllithium (5.0 mL of a 2.5 M solution, 12.5 mmol) was added dropwise and the solution was stirred for 15 min at −78 °C and then slowly warmed to 0 °C. A separate solution of $D_2O$ (501 mg, 25.0 mmol) and THF (25 mL) was prepared under nitrogen in a separate flame-dried round-bottomed flask under nitrogen and sparged with a steady flow of nitrogen gas for 30 minutes. This solution was then added dropwise to the solution of alcohol and butyl lithium at 0º C under nitrogen, and the solution was stirred and slowly warmed to room temperature for three hours. The solution was recooled to 0 °C, quenched with an aqueous saturated ammonium chloride solution, extracted three times with diethyl ether, dried with magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude mixture was purified on silica gel (2:1 pentane:diethyl ether) to give 531.5 mg of the desired labeled alcohol (83% yield, 77.3% D-incorporation by $^1$H-NMR). $R_f$ = 0.72 (2:1 pentane:diethyl ether; stain in CAM). Representative procedure A was then followed to afford the desired labeled acetate (457 mg, 90% yield). $R_f$ = 0.34 (20:1 pentane:diethyl ether, stain in $KMnO_4$).




***d-oct-1-yn-3-yl acetate*.** $^1$H NMR (500 MHz, $CDCl_3$): δ 5.34 (1H, dd (app t), *J* = 6.5 Hz, 6.5 Hz), 2,09 (3H, s), 1.74-1.79 (2H, m), 1.42-1.48 (2H, m), 1.29-1.35 (4H, m), 0.89 (3H, dd (app t), *J* = 7.0 Hz, 7.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 169.9, 81.4, 73.3, 63.8, 34.5, 31.2, 24.5, 24.5, 21.0, 13.9; IR (neat): 3294 (w), 2956 (w), 2931 (m), 2863 (w), 1740 (s), 1371 (m), 1227 (s), 1020 (s), 962 (w), 892 (w) $cm^{-1}$; HRMS-(ESI+) for $C_{10}H_{16}D_1O_2$ [M+H]: calculated:

170.12913, found: 170.12897.

In order to test for the kinetic isotope effect, Representative Procedure **C** was followed on a 0.2 mmol scale with a mixture of labeled and unlabeled oct-1-yn-3-yl acetate as shown below. The change in ratio of labeled and unlabeled acetate in the recovered enriched sample was compared with the ratio in the starting material, and average rates for each were determined.




*1.6.3 Computational Details for DFT Studies*

All calculations were performed using Gaussian 09 with all geometry optimizations, energies and frequencies were calculated at the DFT level utilizing the B3LYP hybrid

functional.[41,42] The 6-31G** basis set was used for the elements C, H, P, and O in conjunction with the LANL2DZ relativistic pseudopotential for Pd. The two oxygens and carbonyl carbon of the acetate group were augmented with diffuse functions. All free energies were calculated at 333.15 K. The PCM model was used to estimate the effect of solvation (THF).[-] The frequency calculations for transition states demonstrated one imaginary frequency each, and were found to connected with the correct ground states through IRC calculations. NBO analysis was carried out with Gaussian NBO version 3.1.[43] The three-dimensional structures presented in Figure 1 were visualized utilizing CYLview.[44]

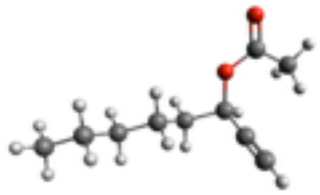
**Substrate_1**

[41] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

[42] a) A. D. Becke*, Phys. Rev. A* **1988**, *38*, 3098; (b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785.

[43] (a) S. Miertus, E. Scrocco, J. Tomassi, *Chem. Phys.* **1981**, *55*, 117. (b) V. Barone, M. Cossi, J. Tomassi, *Chem. Phys.* **1997**, *107*, 3210.

[44] NBO Version 3.1, E. D. Glendening, A. E. Reed, J. E. Carpenter, and F. Weinhold.



---
Cartesian coordinates (Angstroms):
---

| | | | |
|---|---|---|---|
| C | 1.265 | 1.700 | -0.204 |
| C | 1.415 | 2.676 | -0.901 |
| C | 1.093 | 0.523 | 0.655 |
| O | 1.512 | -0.683 | -0.052 |
| C | 2.817 | -1.024 | -0.201 |
| C | 3.880 | -0.170 | 0.449 |
| O | 3.064 | -2.027 | -0.843 |
| H | 3.788 | 0.877 | 0.152 |
| H | 4.855 | -0.552 | 0.152 |
| H | 3.797 | -0.221 | 1.540 |
| C | -1.368 | 0.101 | -0.035 |
| C | -2.798 | -0.107 | 0.480 |
| H | -2.822 | -0.981 | 1.148 |
| C | -3.824 | -0.303 | -0.643 |
| H | -3.093 | 0.755 | 1.095 |
| C | -0.359 | 0.295 | 1.101 |
| H | 1.711 | 0.637 | 1.552 |
| H | -0.644 | 1.158 | 1.715 |
| H | -0.357 | -0.580 | 1.761 |
| H | -1.343 | 0.976 | -0.697 |
| H | -1.070 | -0.761 | -0.644 |
| H | 1.542 | 3.537 | -1.519 |
| H | -3.528 | -1.165 | -1.255 |
| H | -3.796 | 0.568 | -1.311 |
| C | -5.252 | -0.506 | -0.128 |
| H | -5.318 | -1.391 | 0.516 |
| H | -5.958 | -0.642 | -0.953 |
| H | -5.588 | 0.356 | 0.460 |

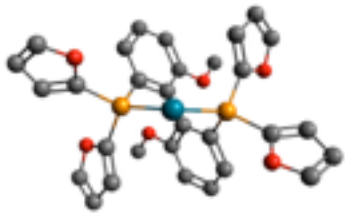
| | 1 | 2 | 3 |
|---|---|---|---|
| | A | A | A |
| Frequencies -- | 40.3369 | 51.3184 | 64.7273 |
| Red. masses -- | 3.7391 | 3.5972 | 1.7560 |

Zero-Point Correction= 0.240889 (Hartree/Particle)

| | |
|---|---|
| Thermal correction to Energy= | 0.258417 |
| Thermal correction to Enthalpy= | 0.259472 |
| Thermal correction to Gibbs Free Energy= | 0.191438 |
| Sum of electronic and zero-point Energies= | -540.887275 |
| Sum of electronic and thermal Energies= | -540.869747 |
| Sum of electronic and thermal Enthalpies= | -540.868692 |
| Sum of electronic and thermal Free Energies= | -540.936726 |

| Item | Value | Threshold | Converged? |
|---|---|---|---|
| Maximum Force | 0.000031 | 0.000450 | YES |
| RMS Force | 0.000006 | 0.000300 | YES |

**Catalyst_a**



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Cartesian coordinates (Angstroms):

---

| | | | |
|---|---|---|---|
| Pd | 0.000 | -2.186 | -0.000 |
| P | 1.930 | -0.943 | -0.041 |
| O | 3.377 | 0.782 | 1.596 |
| O | -1.118 | 3.159 | -1.141 |
| O | 3.482 | -2.436 | -1.696 |
| C | 2.487 | -0.269 | 1.549 |
| C | 2.195 | -0.668 | 2.826 |
| H | 1.518 | -1.467 | 3.094 |
| C | 2.939 | 0.177 | 3.708 |
| H | 2.952 | 0.150 | 4.788 |
| C | 3.635 | 1.034 | 2.909 |
| H | 4.325 | 1.840 | 3.107 |
| C | 1.401 | 0.527 | -1.063 |
| C | 0.330 | 1.363 | -0.677 |
| C | -0.106 | 2.360 | -1.585 |
| C | 0.481 | 2.503 | -2.847 |
| H | 0.135 | 3.261 | -3.538 |
| C | 1.528 | 1.658 | -3.210 |
| H | 1.990 | 1.767 | -4.187 |
| C | 1.987 | 0.684 | -2.331 |

H 2.804 0.040 -2.634
C -1.608 4.182 -2.000
H -0.825 4.906 -2.254
H -2.397 4.687 -1.442
H -2.028 3.764 -2.923
C 3.538 -1.412 -0.771
C 4.758 -2.698 -2.091
H 4.872 -3.482 -2.825
C 5.636 -1.882 -1.444
H 6.711 -1.874 -1.558
C 4.848 -1.047 -0.591
H 5.199 -0.271 0.072
P -1.930 -0.943 0.041
O -3.377 0.782 -1.596
O 1.118 3.159 1.141
O -3.482 -2.436 1.696
C -2.487 -0.269 -1.549
C -2.195 -0.668 -2.826
H -1.518 -1.467 -3.094
C -2.939 0.177 -3.708
H -2.952 0.150 -4.788
C -3.635 1.034 -2.909
H -4.325 1.840 -3.107
C -1.401 0.527 1.063
C -0.330 1.363 0.677
C 0.106 2.360 1.585
C -0.481 2.503 2.847
H -0.135 3.261 3.538
C -1.528 1.658 3.210
H -1.990 1.767 4.187
C -1.987 0.684 2.331
H -2.804 0.040 2.634
C 1.608 4.182 2.000
H 0.825 4.906 2.254
H 2.397 4.687 1.442
H 2.028 3.764 2.923
C -3.538 -1.412 0.771
C -4.758 -2.698 2.091
H -4.872 -3.482 2.825
C -5.636 -1.882 1.444
H -6.711 -1.874 1.558
C -4.848 -1.047 0.591
H -5.199 -0.271 -0.072

| | 1 | 2 | 3 |
|---|---|---|---|
| | A | A | A |
| Frequencies -- | -5.3361 | 22.6076 | 34.1663 |
| Red. masses -- | 6.9580 | 6.1620 | 4.9712 |

Zero-Point Correction= 0.472240 (Hartree/Particle)
Thermal correction to Energy= 0.515390
Thermal correction to Enthalpy= 0.516445
Thermal correction to Gibbs Free Energy= 0.389564
Sum of electronic and zero-point Energies= -2417.878386
Sum of electronic and thermal Energies= -2417.835236
Sum of electronic and thermal Enthalpies= -2417.834180
Sum of electronic and thermal Free Energies= -2417.961062

| Item | Value | Threshold | Converged? |
|---|---|---|---|
| Maximum Force | 0.000000 | 0.000002 | YES |
| RMS Force | 0.000000 | 0.000001 | YES |

**NOTE:** We were unable to optimize the geometry to remove the small negative frequency listed (-5.3361) despite use of Ultrafine integration and Verytight convergence criteria. Its effect on the free energy of the complex should be negligible however the total energy of the unbound catalyst and substrate could be slightly lower than the 4.9 kcal/mol listed in the report.

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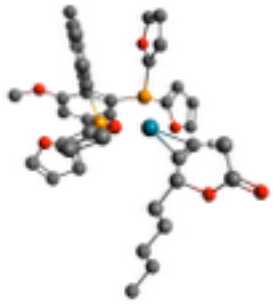
**GS_fast**



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Cartesian coordinates (Angstroms):

---
Pd -0.881  0.905 -0.188
P -0.085 -1.270 -0.771
O  0.575 -3.725  0.344
O  5.018 -0.290 -0.511
O -1.691 -1.426 -2.973
C -0.026 -2.503  0.555
C -0.547 -2.466  1.821
H -1.067 -1.628  2.263
C -0.253 -3.728  2.427
H -0.510 -4.053  3.425
C  0.427 -4.447  1.489
H  0.852 -5.439  1.478
C  1.628 -1.197 -1.482
C  2.736 -0.831 -0.691
C  3.986 -0.633 -1.330
C  4.121 -0.784 -2.714
H  5.077 -0.629 -3.197
C  3.010 -1.139 -3.475
H  3.113 -1.259 -4.550
C  1.774 -1.344 -2.872
H  0.922 -1.617 -3.483
C  6.297 -0.050 -1.088
H  6.686 -0.943 -1.592
H  6.954  0.209 -0.257
H  6.265  0.784 -1.799
C -1.030 -2.188 -2.033
C -2.352 -2.284 -3.800
H -2.913 -1.828 -4.601
C -2.143 -3.574 -3.414
H -2.548 -4.460 -3.883
C -1.284 -3.513 -2.272
H -0.895 -4.343 -1.701
P  1.219  1.729  0.599
O  3.642  2.737 -0.300
O  3.777 -2.792  0.841
O  0.056  3.132  2.624
C  2.345  2.418 -0.640
C  2.127  2.746 -1.952
H  1.203  2.601 -2.492
C  3.350  3.296 -2.450
H  3.547  3.661 -3.448
C  4.229  3.264 -1.409
H  5.260  3.566 -1.297

C 2.188 0.420 1.488
C 2.701 -0.701 0.804
C 3.291 -1.743 1.562
C 3.356 -1.673 2.957
H 3.806 -2.473 3.532
C 2.836 -0.558 3.611
H 2.889 -0.501 4.695
C 2.257 0.480 2.890
H 1.858 1.338 3.419
C 4.376 -3.879 1.538
H 5.254 -3.557 2.111
H 4.688 -4.589 0.771
H 3.661 -4.365 2.212
C 1.154 3.103 1.793
C 0.167 4.241 3.406
H -0.630 4.397 4.117
C 1.301 4.930 3.098
H 1.639 5.850 3.554
C 1.944 4.192 2.055
H 2.875 4.431 1.563
C -2.938 1.258 -0.532
C -2.417 2.335 -0.104
C -4.089 0.480 -1.039
O -5.269 1.342 -1.223
C -5.415 2.147 -2.294
C -4.387 2.095 -3.402
O -6.396 2.872 -2.333
H -3.375 2.230 -3.013
H -4.616 2.880 -4.122
H -4.427 1.126 -3.911
C -4.946 -0.230 1.304
C -5.382 -1.416 2.174
H -2.515 3.368 0.183
H -6.222 -1.935 1.689
C -5.794 -1.009 3.594
H -4.563 -2.147 2.230
C -4.539 -0.658 -0.110
H -3.831 0.041 -2.007
H -3.712 -1.374 -0.059
H -5.375 -1.169 -0.603
H -4.103 0.285 1.783
H -5.764 0.499 1.244
H -6.610 -0.275 3.536
H -4.955 -0.492 4.079

C -6.234 -2.195  4.459
H -7.093 -2.710  4.015
H -6.522 -1.872  5.465
H -5.427 -2.929  4.564

| | 1 | 2 | 3 |
|---|---|---|---|
| | A | A | A |
| Frequencies -- | 5.2435 | 11.4326 | 17.0025 |
| Red. masses -- | 4.9022 | 5.6644 | 4.9356 |

Zero-Point Correction= 0.714784 (Hartree/Particle)
Thermal correction to Energy= 0.778005
Thermal correction to Enthalpy= 0.779060
Thermal correction to Gibbs Free Energy= 0.602667
Sum of electronic and zero-point Energies= -2958.793515
Sum of electronic and thermal Energies= -2958.730294
Sum of electronic and thermal Enthalpies= -2958.729239
Sum of electronic and thermal Free Energies= -2958.905632

| Item | Value | Threshold | Converged? |
|---|---|---|---|
| Maximum Force | 0.000007 | 0.000450 | YES |
| RMS Force | 0.000001 | 0.000300 | YES |

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**GS_slow**

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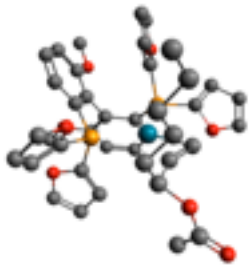

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Cartesian coordinates (Angstroms):

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Pd  0.946  0.559 -0.384
P -0.102 -1.559  0.019
O -1.564 -3.459 -1.382
O -4.753  0.111  1.654
O  1.893 -2.596  1.565
C -0.790 -2.323 -1.472
C -0.650 -1.973 -2.789

H -0.105 -1.114 -3.155
C -1.373 -2.940 -3.554
H -1.484 -2.978 -4.628
C -1.905 -3.812 -2.652
H -2.519 -4.696 -2.746
C -1.502 -1.476  1.238
C -2.678 -0.751  0.958
C -3.638 -0.596  1.990
C -3.429 -1.142  3.260
H -4.165 -1.021  4.044
C -2.256 -1.851  3.513
H -2.092 -2.279  4.498
C -1.299 -2.018  2.518
H -0.393 -2.567  2.741
C -5.755  0.316  2.643
H -6.173 -0.634  2.998
H -6.540  0.894  2.156
H -5.365  0.882  3.497
C  0.916 -2.934  0.652
C  2.552 -3.743  1.897
H  3.350 -3.634  2.616
C  2.034 -4.804  1.218
H  2.365 -5.831  1.281
C  0.972 -4.282  0.414
H  0.323 -4.834 -0.249
P -1.042  1.851 -0.099
O -2.776  2.783  1.860
O -4.492 -2.011 -0.591
O -0.308  3.710 -1.960
C -1.544  2.223  1.601
C -0.852  2.085  2.774
H  0.140  1.667  2.875
C -1.697  2.583  3.815
H -1.480  2.628  4.872
C -2.846  2.989  3.204
H -3.764  3.428  3.565
C -2.491  1.015 -0.901
C -3.025 -0.184 -0.388
C -4.009 -0.865 -1.146
C -4.439 -0.370 -2.382
H -5.189 -0.895 -2.960
C -3.893  0.816 -2.871
H -4.229  1.205 -3.828
C -2.929  1.505 -2.144

H -2.514  2.422 -2.545
C -5.474 -2.754 -1.304
H -6.386 -2.168 -1.466
H -5.707 -3.617 -0.679
H -5.090 -3.102 -2.271
C -1.059  3.526 -0.820
C -0.423  5.020 -2.315
H  0.115  5.315 -3.203
C -1.220  5.686 -1.433
H -1.480  6.734 -1.465
C -1.635  4.718 -0.465
H -2.283  4.878  0.384
C  3.005  0.575 -0.911
C  2.557  1.764 -0.947
C  4.124 -0.380 -1.083
O  5.184  0.197 -1.926
C  5.084  0.258 -3.270
C  3.890 -0.374 -3.949
O  5.984  0.806 -3.885
H  2.703  2.814 -1.134
H  2.952 -0.005 -3.528
H  3.911 -1.462 -3.823
H  3.935 -0.142 -5.013
C  4.804 -0.777  0.237
H  3.769 -1.293 -1.569
C  5.398  0.384  1.043
H  5.588 -1.504 -0.007
H  4.051 -1.301  0.835
C  6.067 -0.081  2.343
H  4.605  1.103  1.280
H  6.132  0.918  0.427
H  5.336 -0.628  2.955
C  6.653  1.072  3.167
H  6.866 -0.800  2.108
H  7.381  1.620  2.554
C  7.322  0.611  4.466
H  5.854  1.789  3.402
H  8.150 -0.078  4.262
H  6.610  0.088  5.115
H  7.727  1.458  5.030

| | 1 | 2 | 3 |
|---|---|---|---|
| | A | A | A |
| Frequencies -- | 8.4054 | 12.0801 | 18.9899 |

Red. masses -- 4.9624 5.2301 5.0644
Zero-Point Correction= 0.715255 (Hartree/Particle)
Thermal correction to Energy= 0.778278
Thermal correction to Enthalpy= 0.779333
Thermal correction to Gibbs Free Energy= 0.604940
Sum of electronic and zero-point Energies= -2958.791720
Sum of electronic and thermal Energies= -2958.728697
Sum of electronic and thermal Enthalpies= -2958.727642
Sum of electronic and thermal Free Energies= -2958.902035

| Item | Value | Threshold | Converged? |
|---|---|---|---|
| Maximum Force | 0.000008 | 0.000450 | YES |
| RMS Force | 0.000001 | 0.000300 | YES |

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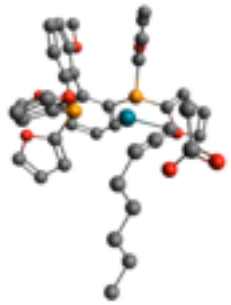
**TS_fast**



---
Cartesian coordinates (Angstroms):
---
Pd -0.897 0.773 -0.095
P 0.049 -1.288 -0.888
O 0.832 -3.783 0.016
O 5.041 0.082 -0.523
O -1.590 -1.265 -3.060
C 0.176 -2.615 0.331
C -0.330 -2.703 1.600
H -0.884 -1.931 2.113
C 0.032 -3.993 2.099
H -0.196 -4.409 3.070
C 0.734 -4.600 1.100
H 1.206 -5.567 1.005
C 1.744 -1.032 -1.586
C 2.814 -0.632 -0.761
C 4.047 -0.293 -1.372

C  4.199 -0.347 -2.762
H  5.142 -0.086 -3.226
C  3.125 -0.743 -3.556
H  3.245 -0.789 -4.634
C  1.905 -1.082 -2.980
H  1.080 -1.385 -3.614
C  6.308  0.438 -1.068
H  6.761 -0.398 -1.613
H  6.936  0.696 -0.215
H  6.226  1.305 -1.734
C -0.881 -2.098 -2.222
C -2.246 -2.055 -3.955
H -2.847 -1.539 -4.687
C -1.984 -3.371 -3.712
H -2.374 -4.216 -4.261
C -1.098 -3.400 -2.590
H -0.669 -4.271 -2.117
P  1.094  1.695  0.720
O  3.364  2.955 -0.214
O  3.995 -2.614  0.632
O -0.182  2.893  2.807
C  2.092  2.533 -0.529
C  1.790  2.906 -1.812
H  0.862  2.703 -2.326
C  2.936  3.593 -2.320
H  3.058  4.026 -3.302
C  3.855  3.591 -1.313
H  4.856  3.983 -1.221
C  2.158  0.402  1.503
C  2.762 -0.616  0.739
C  3.428 -1.664  1.423
C  3.479 -1.695  2.821
H  3.986 -2.499  3.339
C  2.870 -0.677  3.553
H  2.914 -0.698  4.637
C  2.212  0.364  2.907
H  1.743  1.144  3.494
C  4.693 -3.692  1.248
H  5.539 -3.334  1.845
H  5.065 -4.311  0.431
H  4.028 -4.290  1.881
C  0.917  2.986  1.983
C -0.144  3.961  3.651
H -0.952  4.024  4.364

C  0.944  4.739  3.389
H  1.220  5.651  3.898
C  1.635  4.107  2.309
H  2.548  4.435  1.834
C -3.051  1.380 -0.270
C -2.299  2.266  0.241
C -3.768  0.364 -0.851
O -5.750  1.183 -1.255
C -5.995  2.158 -2.058
C -4.840  2.671 -2.926
O -7.124  2.685 -2.180
H -2.281  3.262  0.649
H -4.547  1.897 -3.646
H -3.962  2.898 -2.314
H -5.140  3.564 -3.477
C -4.326 -0.813 -0.090
H -3.662  0.239 -1.922
C -4.532 -0.598  1.411
H -3.646 -1.660 -0.263
H -5.272 -1.077 -0.571
C -5.134 -1.829  2.101
H -5.189  0.267  1.561
H -3.572 -0.347  1.883
H -6.095 -2.076  1.628
C -5.349 -1.637  3.608
H -4.480 -2.697  1.936
H -5.999 -0.766  3.770
H -4.388 -1.392  4.082
C -5.959 -2.865  4.291
H -6.937 -3.111  3.860
H -6.101 -2.697  5.363
H -5.316 -3.744  4.173

| | 1 | 2 | 3 |
|---|---|---|---|
| | A | A | A |
| Frequencies -- | -194.4801 | 6.5895 | 11.6546 |
| Red. masses -- | 8.7635 | 5.8913 | 4.9555 |

Zero-Point Correction= 0.711575 (Hartree/Particle)
Thermal correction to Energy= 0.775414
Thermal correction to Enthalpy= 0.776469
Thermal correction to Gibbs Free Energy= 0.596432
Sum of electronic and zero-point Energies= -2958.768253
Sum of electronic and thermal Energies= -2958.704415
Sum of electronic and thermal Enthalpies= -2958.703360

Sum of electronic and thermal Free Energies= -2958.883396

| Item | Value | Threshold | Converged? |
|---|---|---|---|
| Maximum Force | 0.000003 | 0.000450 | YES |
| RMS Force | 0.000001 | 0.000300 | YES |

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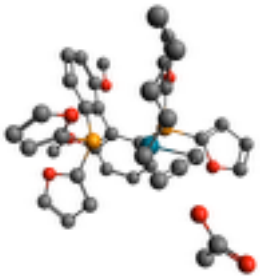
**TS_Slow**



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Cartesian coordinates (Angstroms):
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| | | | |
|---|---|---|---|
| Pd | 0.938 | 0.566 | -0.158 |
| P | -0.228 | -1.477 | -0.703 |
| O | -1.785 | -2.511 | -2.743 |
| O | -4.753 | -0.341 | 1.585 |
| O | 1.716 | -3.130 | 0.253 |
| C | -0.932 | -1.498 | -2.365 |
| C | -0.730 | -0.653 | -3.424 |
| H | -0.113 | 0.234 | -3.415 |
| C | -1.497 | -1.168 | -4.515 |
| H | -1.580 | -0.757 | -5.511 |
| C | -2.114 | -2.289 | -4.045 |
| H | -2.785 | -3.009 | -4.490 |
| C | -1.614 | -1.812 | 0.482 |
| C | -2.739 | -0.968 | 0.548 |
| C | -3.688 | -1.187 | 1.578 |
| C | -3.511 | -2.212 | 2.513 |
| H | -4.237 | -2.377 | 3.299 |
| C | -2.387 | -3.031 | 2.428 |
| H | -2.251 | -3.829 | 3.151 |
| C | -1.442 | -2.837 | 1.426 |
| H | -0.573 | -3.482 | 1.382 |
| C | -5.749 | -0.502 | 2.590 |
| H | -6.227 | -1.487 | 2.528 |

H -6.493  0.272  2.399
H -5.332 -0.363  3.594
C  0.728 -3.024 -0.701
C  2.311 -4.345  0.083
H  3.112 -4.577  0.769
C  1.741 -5.015 -0.957
H  2.016 -5.994 -1.320
C  0.711 -4.161 -1.465
H  0.037 -4.365 -2.283
P -0.948  1.737  0.592
O -2.597  1.897  2.798
O -4.621 -1.389 -1.335
O -0.099  4.118 -0.436
C -1.406  1.412  2.306
C -0.722  0.774  3.307
H  0.240  0.294  3.207
C -1.532  0.867  4.480
H -1.312  0.473  5.462
C -2.652  1.554  4.114
H -3.538  1.868  4.645
C -2.420  1.373 -0.465
C -3.041  0.108 -0.452
C -4.062 -0.151 -1.400
C -4.445  0.821 -2.330
H -5.225  0.618 -3.052
C -3.814  2.063 -2.323
H -4.113  2.820 -3.043
C -2.808  2.343 -1.405
H -2.325  3.313 -1.424
C -5.639 -1.730 -2.272
H -6.512 -1.075 -2.174
H -5.928 -2.754 -2.037
H -5.264 -1.686 -3.301
C -0.818  3.548  0.590
C -0.099  5.464 -0.229
H  0.431  6.052 -0.963
C -0.790  5.773  0.904
H -0.947  6.761  1.313
C -1.260  4.531  1.436
H -1.854  4.384  2.325
C  3.135  1.115 -0.452
C  2.388  2.016  0.042
C  3.920  0.139 -1.004
O  5.832  1.104 -1.507

C 5.968 2.058 -2.359
C 4.752 2.420 -3.220
O 7.038 2.686 -2.529
H 2.381 3.043 0.366
H 3.890 2.658 -2.589
H 4.472 1.568 -3.850
H 4.976 3.273 -3.863
C 4.594 -0.946 -0.205
H 3.810 -0.043 -2.068
C 4.868 -0.613 1.264
H 5.526 -1.186 -0.725
H 3.959 -1.839 -0.277
C 5.594 -1.749 1.996
H 3.921 -0.396 1.774
H 5.470 0.302 1.316
H 4.997 -2.670 1.927
C 5.875 -1.439 3.472
H 6.544 -1.963 1.485
H 6.471 -0.519 3.539
C 6.603 -2.574 4.198
H 4.926 -1.225 3.983
H 7.571 -2.787 3.729
H 6.016 -3.499 4.178
H 6.791 -2.323 5.247

| | 1 | 2 | 3 |
|---|---|---|---|
| | A | A | A |
| Frequencies -- | -176.4829 | 10.9015 | 16.0793 |
| Red. masses -- | 9.4646 | 5.6090 | 4.7760 |

Zero-Point Correction= 0.712071 (Hartree/Particle)
Thermal correction to Energy= 0.775633
Thermal correction to Enthalpy= 0.776688
Thermal correction to Gibbs Free Energy= 0.600204
Sum of electronic and zero-point Energies= -2958.766716
Sum of electronic and thermal Energies= -2958.703153
Sum of electronic and thermal Enthalpies= -2958.702098
Sum of electronic and thermal Free Energies= -2958.878582

| Item | Value | Threshold | Converged? |
|---|---|---|---|
| Maximum Force | 0.000004 | 0.000450 | YES |
| RMS Force | 0.000001 | 0.000300 | YES |

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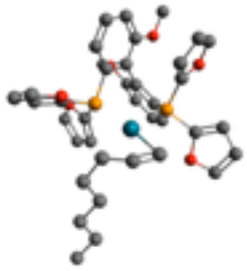
**Int_a_fast**



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Cartesian coordinates (Angstroms):
---
Pd -1.057  0.764 -1.147
P -0.478 -1.450 -0.553
O -0.460 -3.155  1.599
O  4.501 -0.593  0.611
O -1.464 -2.463 -2.887
C -0.906 -1.944  1.124
C -1.673 -1.329  2.078
H -2.145 -0.362  1.984
C -1.704 -2.206  3.205
H -2.211 -2.047  4.145
C -0.954 -3.292  2.860
H -0.688 -4.204  3.372
C  1.335 -1.703 -0.787
C  2.272 -1.096  0.071
C  3.648 -1.203 -0.251
C  4.065 -1.896 -1.393
H  5.117 -1.979 -1.635
C  3.116 -2.489 -2.224
H  3.443 -3.030 -3.107
C  1.759 -2.394 -1.933
H  1.038 -2.855 -2.597
C  5.902 -0.664  0.354
H  6.259 -1.700  0.357
H  6.380 -0.115  1.166
H  6.156 -0.193 -0.602
C -1.275 -2.737 -1.551
C -2.088 -3.546 -3.433
H -2.301 -3.481 -4.489
C -2.308 -4.498 -2.485

H -2.787 -5.455 -2.634
C -1.780 -3.977 -1.263
H -1.767 -4.461 -0.298
P  0.815  1.767 -0.136
O  3.437  2.322 -0.715
O  2.709 -2.303  2.451
O -0.741  3.789  0.817
C  2.234  1.904 -1.234
C  2.357  1.704 -2.584
H  1.576  1.370 -3.250
C  3.711  2.015 -2.919
H  4.171  1.968 -3.895
C  4.316  2.381 -1.753
H  5.317  2.697 -1.503
C  1.357  0.901  1.397
C  1.906 -0.394  1.344
C  2.184 -1.057  2.566
C  1.918 -0.438  3.792
H  2.134 -0.945  4.724
C  1.372  0.844  3.815
H  1.170  1.322  4.768
C  1.087  1.514  2.630
H  0.661  2.510  2.668
C  3.032 -3.024  3.638
H  3.785 -2.497  4.235
H  3.440 -3.978  3.302
H  2.141 -3.205  4.250
C  0.519  3.482  0.358
C -0.747  5.120  1.107
H -1.678  5.514  1.484
C  0.470  5.674  0.842
H  0.748  6.709  0.972
C  1.295  4.611  0.357
H  2.329  4.671  0.054
C -2.688  1.634 -2.354
C -1.862  2.554 -2.099
C -3.121  0.329 -2.254
H -1.565  3.581 -2.197
C -4.278 -0.110 -1.381
H -2.877 -0.333 -3.083
C -4.573  0.775 -0.167
H -4.086 -1.143 -1.067
H -5.168 -0.162 -2.027
C -5.732  0.244  0.685

H -4.801  1.795 -0.504
H -3.668  0.853  0.451
H -6.634  0.163  0.062
C -6.037  1.121  1.906
H -5.500 -0.777  1.020
H -6.268  2.141  1.570
H -5.133  1.203  2.526
C -7.194  0.588  2.757
H -8.119  0.527  2.173
H -7.386  1.235  3.619
H -6.976 -0.417  3.137

| | 1 | 2 | 3 |
|---|---|---|---|
| | A | A | A |
| Frequencies -- | 14.3270 | 19.5236 | 26.7237 |
| Red. masses -- | 4.7847 | 5.0831 | 4.6796 |

Zero-Point Correction= 0.662836 (Hartree/Particle)
Thermal correction to Energy= 0.719956
Thermal correction to Enthalpy= 0.721011
Thermal correction to Gibbs Free Energy= 0.562299
Sum of electronic and zero-point Energies= -2730.194948
Sum of electronic and thermal Energies= -2730.137828
Sum of electronic and thermal Enthalpies= -2730.136773
Sum of electronic and thermal Free Energies= -2730.295485

| Item | Value | Threshold | Converged? |
|---|---|---|---|
| Maximum Force | 0.000012 | 0.000450 | YES |
| RMS Force | 0.000002 | 0.000300 | YES |

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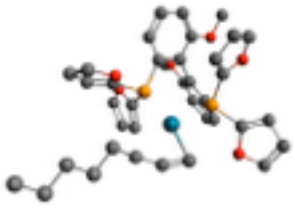
**Int_a_slow**



---
Cartesian coordinates (Angstroms):
---
Pd  0.970  1.148 -0.303
P  0.612 -1.183  0.002
O  0.172 -3.411 -1.544

O -4.449 -1.221  1.121
O  2.533 -1.386  1.913
C  0.454 -2.065 -1.559
C  0.562 -1.631 -2.854
H  0.764 -0.618 -3.169
C  0.335 -2.770 -3.686
H  0.340 -2.805 -4.766
C  0.105 -3.816 -2.841
H -0.108 -4.863 -2.996
C -0.840 -1.653  1.043
C -2.148 -1.303  0.657
C -3.213 -1.589  1.546
C -2.973 -2.213  2.776
H -3.789 -2.434  3.452
C -1.670 -2.555  3.130
H -1.485 -3.044  4.082
C -0.606 -2.276  2.279
H  0.398 -2.545  2.580
C -5.571 -1.487  1.959
H -5.688 -2.560  2.143
H -6.441 -1.116  1.416
H -5.489 -0.959  2.916
C  2.019 -2.003  0.795
C  3.581 -2.146  2.342
H  4.090 -1.789  3.224
C  3.755 -3.224  1.527
H  4.508 -3.991  1.626
C  2.739 -3.135  0.522
H  2.558 -3.825 -0.288
P -1.266  1.759  0.045
O -3.178  1.797  2.013
O -3.307 -2.834 -1.239
O -1.120  3.991 -1.532
C -1.834  1.677  1.749
C -1.138  1.581  2.925
H -0.068  1.473  3.022
C -2.105  1.641  3.975
H -1.921  1.591  5.038
C -3.318  1.770  3.366
H -4.329  1.853  3.735
C -2.292  0.646 -1.008
C -2.500 -0.704 -0.671
C -3.143 -1.541 -1.618
C -3.566 -1.036 -2.852

H -4.058 -1.677 -3.572
C -3.352  0.307 -3.156
H -3.686  0.699 -4.113
C -2.717  1.148 -2.249
H -2.550  2.186 -2.510
C -3.959 -3.735 -2.133
H -4.985 -3.415 -2.346
H -3.979 -4.697 -1.619
H -3.404 -3.837 -3.072
C -1.734  3.444 -0.428
C -1.622  5.250 -1.686
H -1.233  5.810 -2.522
C -2.532  5.524 -0.711
H -3.082  6.445 -0.584
C -2.608  4.353  0.106
H -3.234  4.201  0.972
C  2.727  2.330 -0.959
C  1.776  3.121 -0.700
C  3.286  1.078 -1.054
H  1.394  4.123 -0.691
H  3.266  0.610 -2.039
C  4.339  0.564 -0.101
H  4.176  0.977  0.899
C  5.765  0.907 -0.585
H  4.242 -0.524 -0.033
H  5.869  1.998 -0.657
H  5.910  0.513 -1.599
C  6.848  0.343  0.345
H  6.699  0.742  1.358
C  8.273  0.663 -0.123
H  6.726 -0.746  0.424
H  8.391  1.752 -0.204
H  8.420  0.264 -1.135
C  9.351  0.101  0.810
H  9.252  0.510  1.822
H 10.356  0.344  0.450
H  9.280 -0.990  0.885

| | 1 | 2 | 3 |
|---|---|---|---|
| | A | A | A |
| Frequencies -- | 12.3881 | 16.5233 | 22.1060 |
| Red. masses -- | 5.2689 | 5.5854 | 4.6623 |

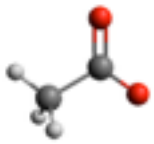
Zero-Point Correction= 0.663041 (Hartree/Particle)
Thermal correction to Energy= 0.720293

Thermal correction to Enthalpy= 0.721348
Thermal correction to Gibbs Free Energy= 0.561572
Sum of electronic and zero-point Energies= -2730.193044
Sum of electronic and thermal Energies= -2730.135792
Sum of electronic and thermal Enthalpies= -2730.134737
Sum of electronic and thermal Free Energies= -2730.294513

| Item | Value | Threshold | Converged? |
|---|---|---|---|
| Maximum Force | 0.000033 | 0.000450 | YES |
| RMS Force | 0.000005 | 0.000300 | YES |

---

**OAc**



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Cartesian coordinates (Angstroms):
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O -0.803 -1.108 0.002
C -0.191 -0.000 -0.008
O -0.721 1.150 0.002
C 1.353 -0.039 -0.003
H 1.741 -1.032 -0.243
H 1.715 0.241 0.994
H 1.757 0.692 -0.710

| | 1 | 2 | 3 |
|---|---|---|---|
| | A | A | A |
| Frequencies -- | 50.4181 | 447.5707 | 611.1940 |
| Red. masses -- | 1.0873 | 3.0453 | 2.7933 |

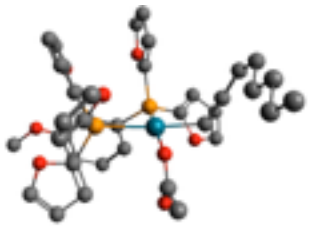
Zero-Point Correction= 0.048453 (Hartree/Particle)
Thermal correction to Energy= 0.053585
Thermal correction to Enthalpy= 0.054640
Thermal correction to Gibbs Free Energy= 0.017244
Sum of electronic and zero-point Energies= -228.578257
Sum of electronic and thermal Energies= -228.573125
Sum of electronic and thermal Enthalpies= -228.572070
Sum of electronic and thermal Free Energies= -228.609466

| Item | Value | Threshold | Converged? |
|---|---|---|---|
| Maximum Force | 0.000001 | 0.000015 | YES |

| | | | | |
|---|---|---|---|---|
| RMS | Force | 0.000000 | 0.000010 | YES |

---

**Int_b_fast**



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Cartesian coordinates (Angstroms):

---

| | | | |
|---|---|---|---|
| Pd | 1.024 | 0.191 | -0.623 |
| P | -0.327 | -1.677 | 0.233 |
| O | -2.136 | -3.591 | -0.600 |
| O | -4.522 | 0.947 | 1.737 |
| O | 1.686 | -2.418 | 1.918 |
| C | -1.178 | -2.685 | -0.995 |
| C | -1.011 | -2.745 | -2.354 |
| H | -0.302 | -2.157 | -2.921 |
| C | -1.919 | -3.744 | -2.827 |
| H | -2.067 | -4.063 | -3.849 |
| C | -2.573 | -4.217 | -1.727 |
| H | -3.339 | -4.964 | -1.583 |
| C | -1.588 | -1.192 | 1.494 |
| C | -2.651 | -0.342 | 1.136 |
| C | -3.515 | 0.132 | 2.152 |
| C | -3.316 | -0.235 | 3.488 |
| H | -3.977 | 0.127 | 4.266 |
| C | -2.257 | -1.079 | 3.818 |
| H | -2.107 | -1.367 | 4.854 |
| C | -1.394 | -1.555 | 2.836 |
| H | -0.574 | -2.205 | 3.115 |
| C | -5.423 | 1.468 | 2.708 |
| H | -5.964 | 0.668 | 3.226 |
| H | -6.133 | 2.083 | 2.155 |
| H | -4.902 | 2.090 | 3.445 |
| C | 0.715 | -2.903 | 1.073 |
| C | 2.395 | -3.489 | 2.373 |
| H | 3.196 | -3.263 | 3.060 |
| C | 1.908 | -4.644 | 1.841 |
| H | 2.278 | -5.643 | 2.025 |

C  0.816 -4.266  0.997
H  0.184 -4.920  0.413
P -0.677  1.734 -0.433
O -2.035  3.166  1.489
O -4.723 -1.530 -0.111
O -0.004  3.154 -2.671
C -0.936  2.379  1.229
C -0.157  2.290  2.352
H  0.771  1.743  2.435
C -0.810  3.059  3.364
H -0.485  3.212  4.383
C -1.939  3.563  2.788
H -2.738  4.193  3.147
C -2.257  0.979 -1.034
C -2.967  0.023 -0.283
C -4.080 -0.617 -0.886
C -4.462 -0.312 -2.196
H -5.311 -0.805 -2.654
C -3.741  0.637 -2.918
H -4.038  0.874 -3.935
C -2.646  1.279 -2.351
H -2.094  2.002 -2.937
C -5.848 -2.216 -0.652
H -6.651 -1.520 -0.922
H -6.198 -2.882  0.137
H -5.570 -2.810 -1.531
C -0.506  3.264 -1.396
C  0.068  4.414 -3.185
H  0.446  4.487 -4.193
C -0.371  5.326 -2.274
H -0.421  6.397 -2.408
C -0.747  4.582 -1.111
H -1.148  4.972 -0.188
C  2.320  1.698 -1.129
C  3.061  2.276 -0.235
H  2.384  1.896 -2.196
C  3.787  2.866  0.700
H  3.414  3.799  1.130
C  5.122  2.392  1.236
H  5.034  2.260  2.326
H  5.855  3.203  1.108
C  5.666  1.106  0.608
H  4.937  0.298  0.747
C  7.022  0.680  1.184

H 5.757 1.246 -0.478
H 6.929 0.537 2.271
H 7.751 1.491 1.046
C 7.572 -0.605 0.552
O 2.610 -1.188 -1.048
C 2.690 -1.588 -2.272
C 3.885 -2.490 -2.577
O 1.899 -1.283 -3.188
H 4.647 -1.898 -3.098
H 3.583 -3.301 -3.245
H 4.328 -2.900 -1.668
H 7.667 -0.461 -0.533
H 6.842 -1.415 0.688
C 8.925 -1.034 1.130
H 9.684 -0.258 0.978
H 9.290 -1.953 0.659
H 8.854 -1.219 2.209

| | 1 | 2 | 3 |
|---|---|---|---|
| | A | A | A |
| Frequencies -- | 9.7552 | 14.4047 | 16.6158 |
| Red. masses -- | 4.6377 | 5.3024 | 4.4413 |

Zero-Point Correction= 0.712960 (Hartree/Particle)
Thermal correction to Energy= 0.776930
Thermal correction to Enthalpy= 0.777985
Thermal correction to Gibbs Free Energy= 0.600612
Sum of electronic and zero-point Energies= -2958.804431
Sum of electronic and thermal Energies= -2958.740461
Sum of electronic and thermal Enthalpies= -2958.739406
Sum of electronic and thermal Free Energies= -2958.916780

| Item | Value | Threshold | Converged? |
|---|---|---|---|
| Maximum Force | 0.000005 | 0.000450 | YES |
| RMS Force | 0.000001 | 0.000300 | YES |

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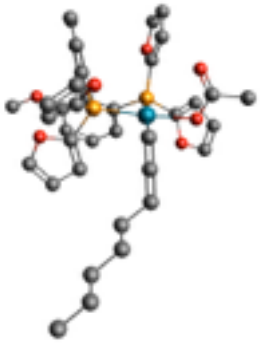
**Int_b_slow**



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Cartesian coordinates (Angstroms):
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Pd  0.361  1.367  0.509
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O -4.515  0.946 -0.136
O -1.973 -3.958 -1.203
O -1.004  2.905 -2.590
C -3.288  1.283  0.391
C -3.439  1.708  1.685
H -2.638  2.059  2.322
C -4.836  1.627  1.977
H -5.327  1.881  2.905
C -5.435  1.159  0.844
H -6.459  0.935  0.584
C -1.961 -0.348 -1.659
C -1.984 -1.614 -1.043
C -1.948 -2.768 -1.862
C -1.889 -2.656 -3.255
H -1.861 -3.539 -3.881
C -1.868 -1.392 -3.842
H -1.828 -1.306 -4.924
C -1.901 -0.243 -3.058
H -1.878  0.729 -3.535
C -1.965 -5.161 -1.965
H -2.838 -5.224 -2.626
H -2.003 -5.973 -1.239
H -1.050 -5.251 -2.562
C -2.070  2.550 -1.797
C -1.387  3.992 -3.316
H -0.648  4.385 -3.998
C -2.666  4.346 -3.007
H -3.225  5.169 -3.428

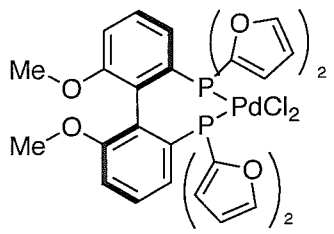
C -3.112  3.409 -2.021
H -4.081  3.374 -1.545
P  0.548 -0.900  0.887
O  1.171 -3.211 -0.474
O -4.359 -2.386 -0.031
O  1.666 -0.648  3.370
C  1.193 -1.836 -0.511
C  1.796 -1.415 -1.666
H  1.955 -0.386 -1.956
C  2.164 -2.593 -2.386
H  2.659 -2.647 -3.345
C  1.762 -3.647 -1.620
H  1.820 -4.718 -1.740
C -1.090 -1.615  1.367
C -2.131 -1.801  0.437
C -3.397 -2.224  0.916
C -3.611 -2.446  2.280
H -4.580 -2.768  2.642
C -2.567 -2.249  3.180
H -2.734 -2.420  4.240
C -1.316 -1.836  2.737
H -0.524 -1.677  3.458
C -5.660 -2.794  0.379
H -5.641 -3.778  0.861
H -6.254 -2.851 -0.534
H -6.112 -2.063  1.060
C  1.670 -1.404  2.222
C  2.590 -1.190  4.212
H  2.700 -0.699  5.166
C  3.188 -2.269  3.633
H  3.960 -2.887  4.067
C  2.590 -2.411  2.341
H  2.809 -3.165  1.600
C  2.270  1.613  1.224
C  3.259  1.758  0.398
H  2.359  1.679  2.305
C  4.238  1.898 -0.479
O  0.241  3.503  0.374
C -0.264  4.093  1.404
C -0.305  5.619  1.321
O -0.698  3.523  2.425
H  0.362  6.035  2.084
H -1.317  5.971  1.543
H  0.003  5.985  0.340

C  5.139  0.783 -0.963
H  4.451  2.895 -0.871
H  4.764 -0.179 -0.595
C  6.608  0.966 -0.534
H  5.100  0.740 -2.062
H  6.659  0.988  0.563
H  6.965  1.947 -0.877
C  7.535 -0.131 -1.072
H  7.172 -1.112 -0.733
C  8.999  0.041 -0.647
H  7.477 -0.149 -2.170
H  9.056  0.059  0.450
H  9.361  1.021 -0.986
C  9.918 -1.059 -1.187
H  9.603 -2.048 -0.834
H 10.955 -0.907 -0.869
H  9.907 -1.081 -2.283

| | 1 | 2 | 3 |
|---|---|---|---|
| | A | A | A |
| Frequencies -- | 5.1206 | 11.6651 | 20.7114 |
| Red. masses -- | 4.8031 | 5.1055 | 5.6206 |

Zero-Point Correction= 0.713120 (Hartree/Particle)
Thermal correction to Energy= 0.777116
Thermal correction to Enthalpy= 0.778171
Thermal correction to Gibbs Free Energy= 0.599940
Sum of electronic and zero-point Energies= -2958.805039
Sum of electronic and thermal Energies= -2958.741042
Sum of electronic and thermal Enthalpies= -2958.739987
Sum of electronic and thermal Free Energies= -2958.918219

| Item | Value | Threshold | Converged? |
|---|---|---|---|
| Maximum Force | 0.000024 | 0.000450 | YES |
| RMS Force | 0.000002 | 0.000300 | YES |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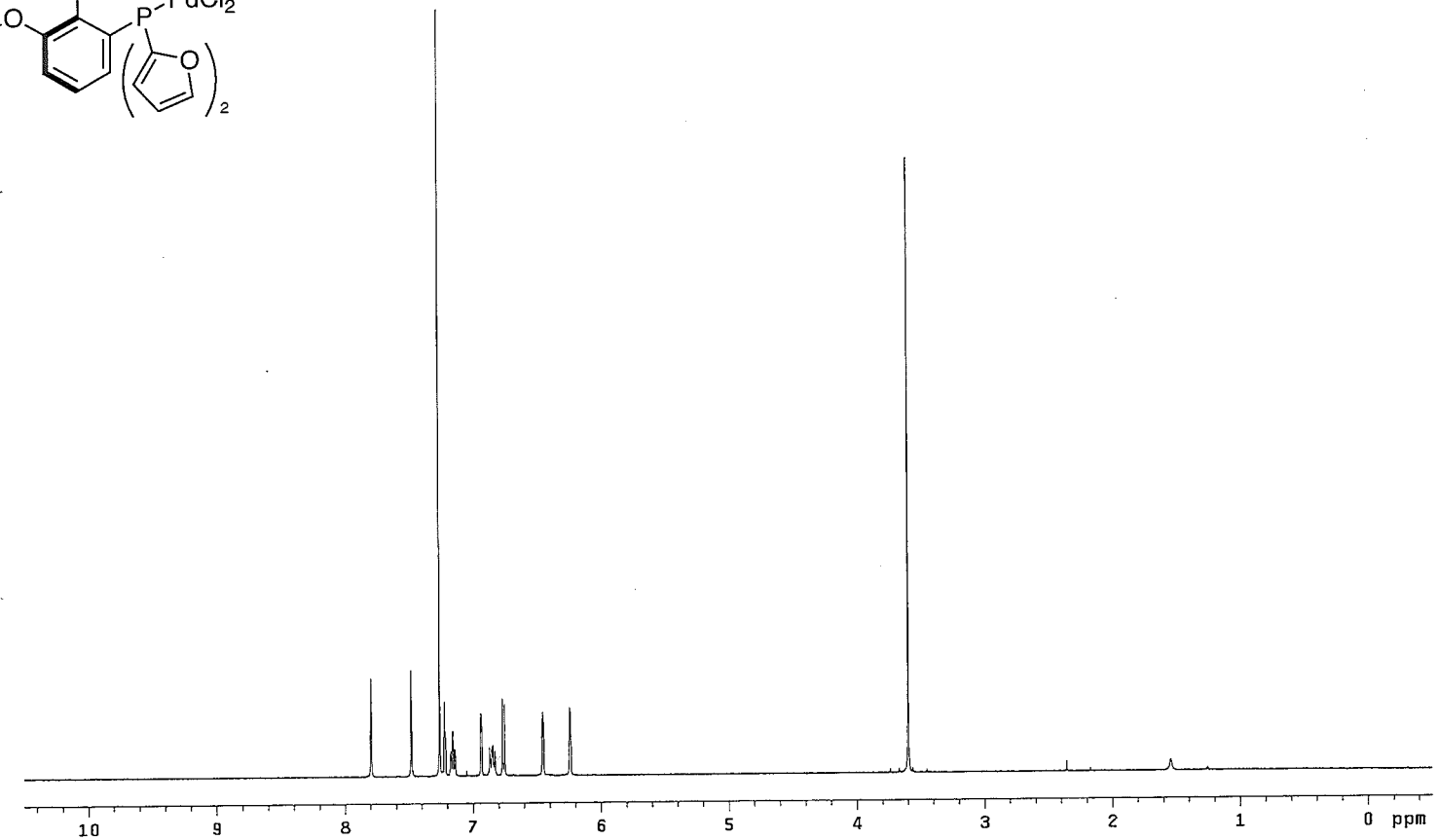
P
P
PdCl2
O
2
O
2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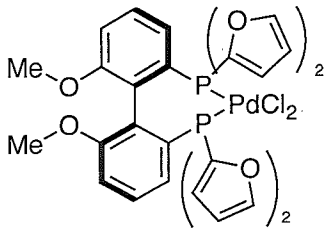
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Me
O
P
P
PdCl2
O
O
2
2


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40
20
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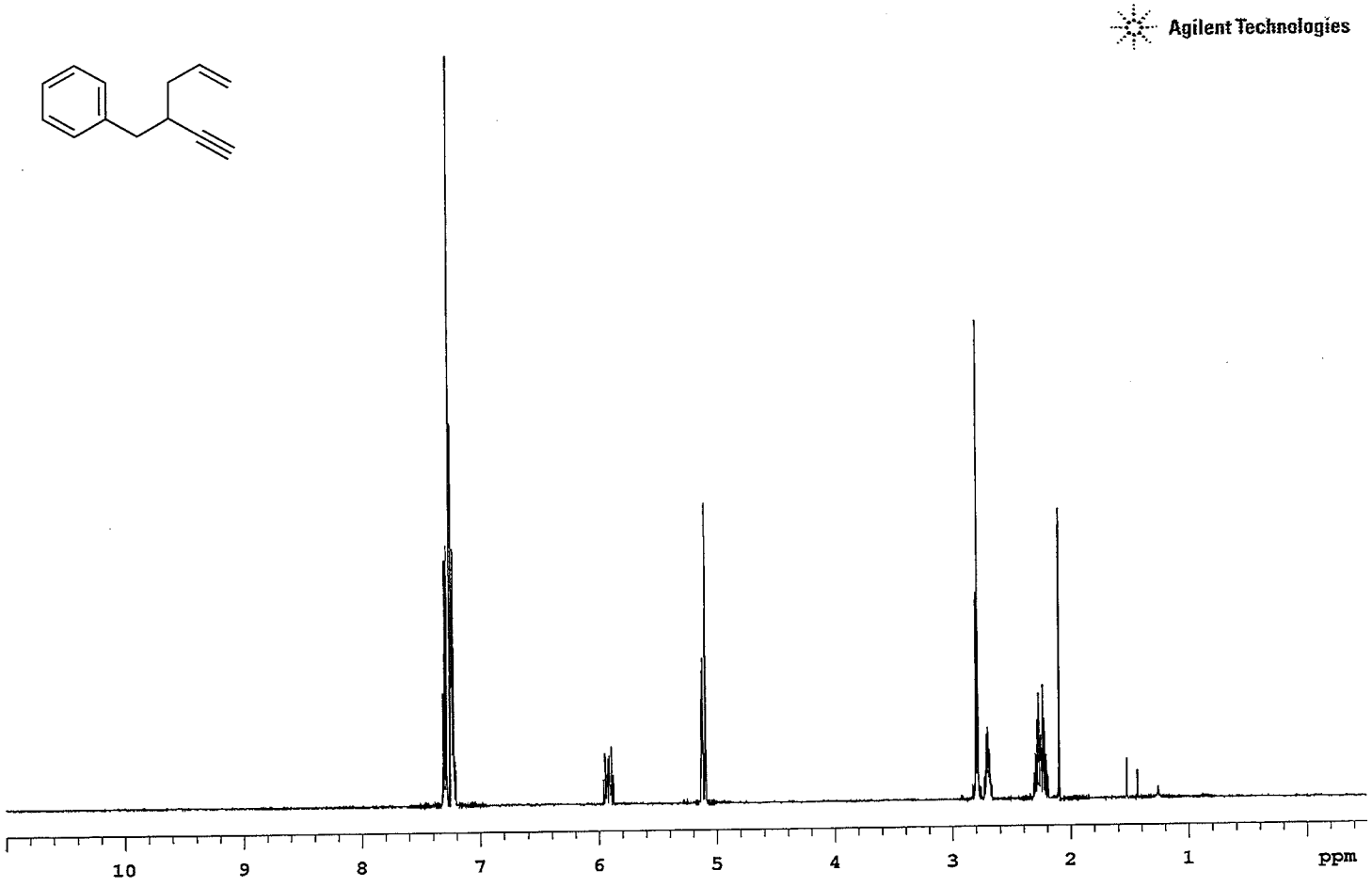
ppm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3
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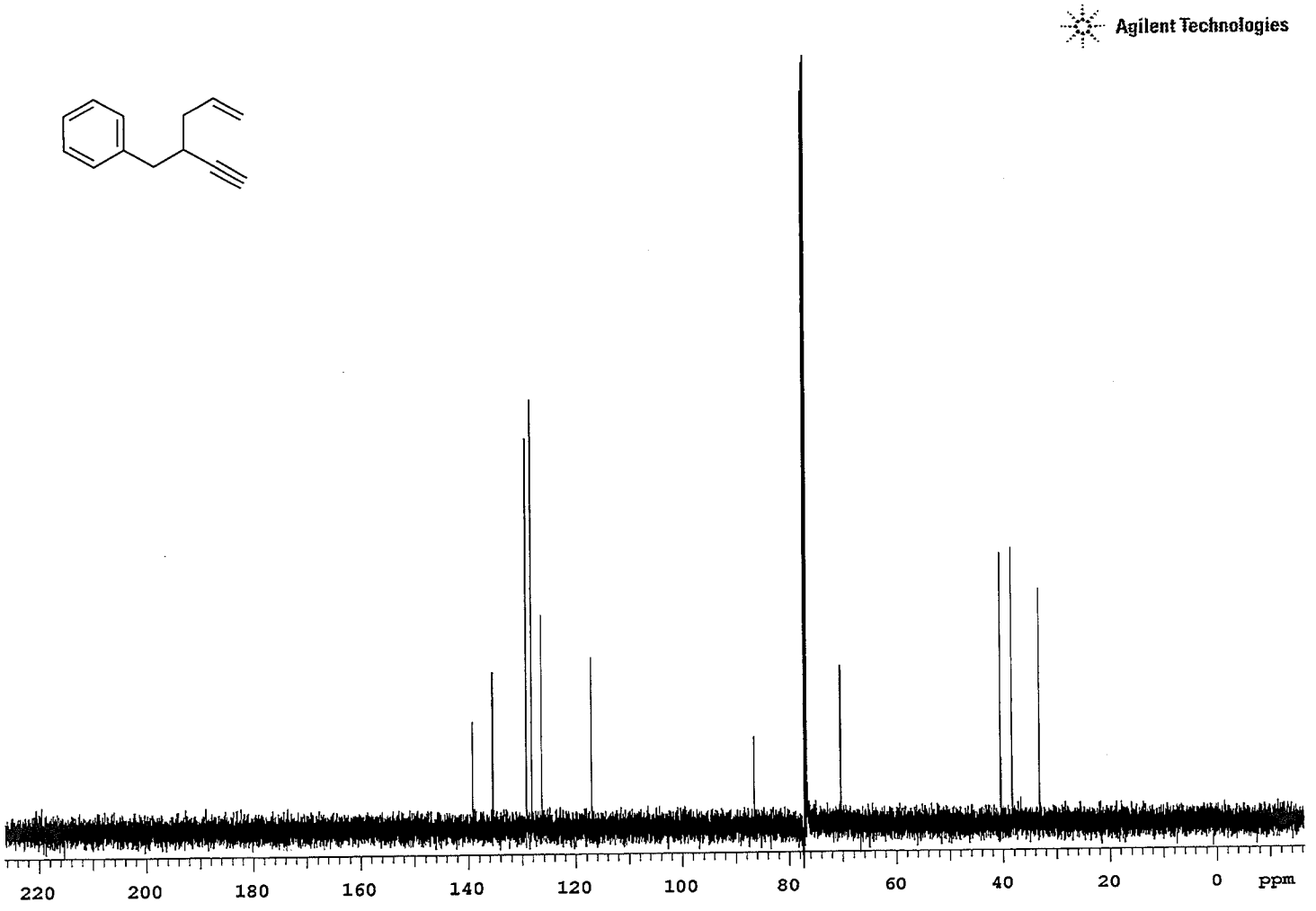
ppm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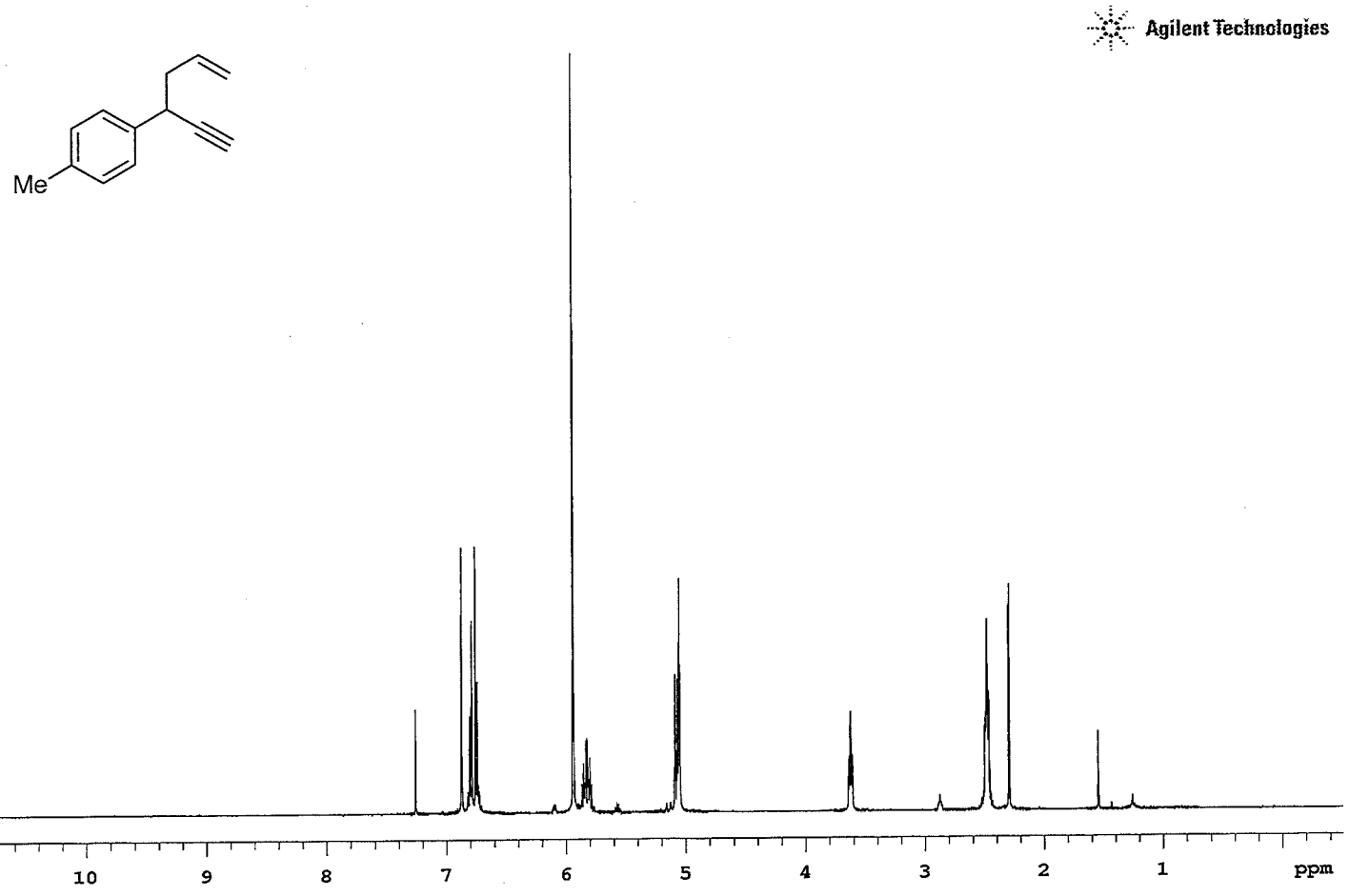
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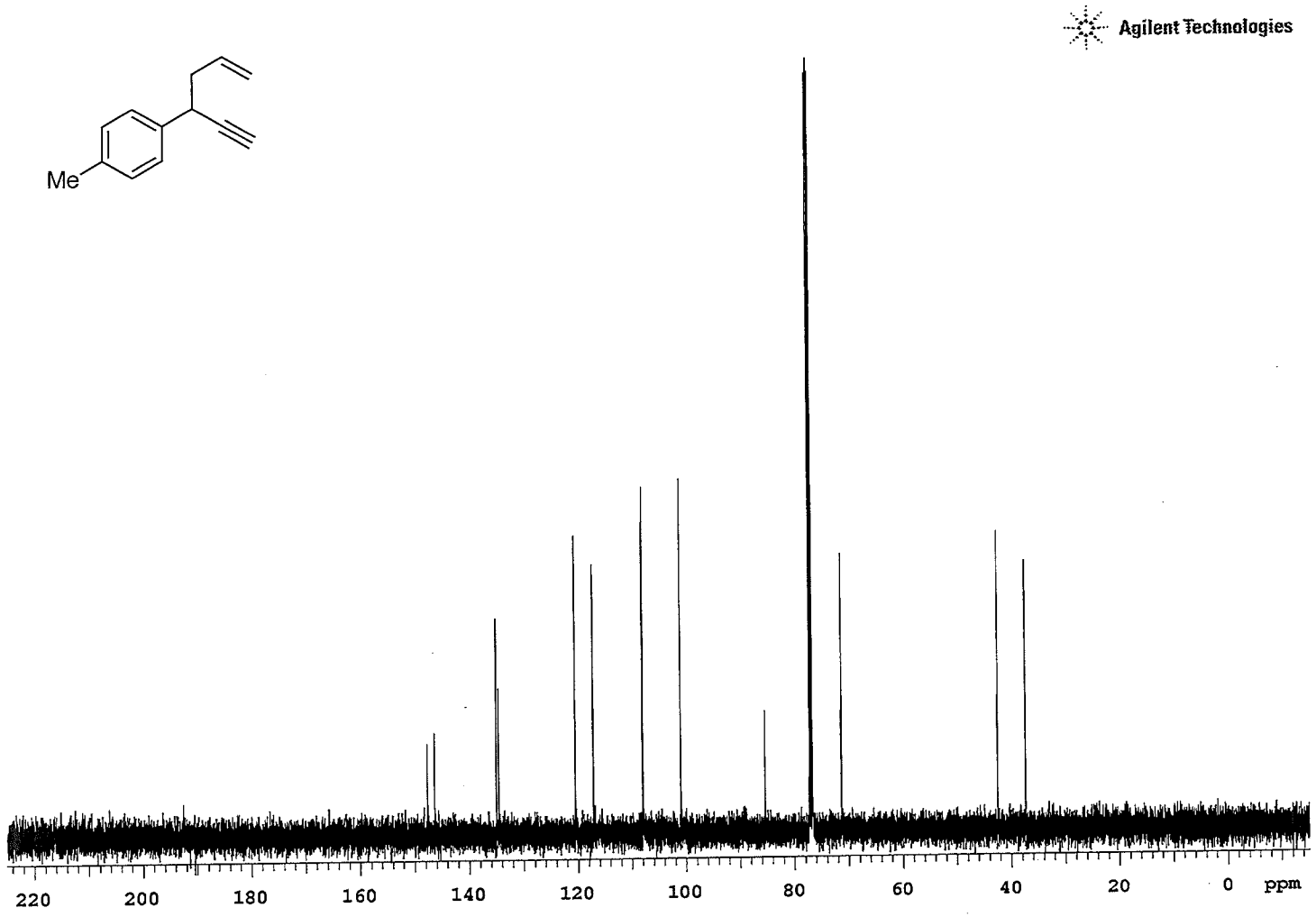
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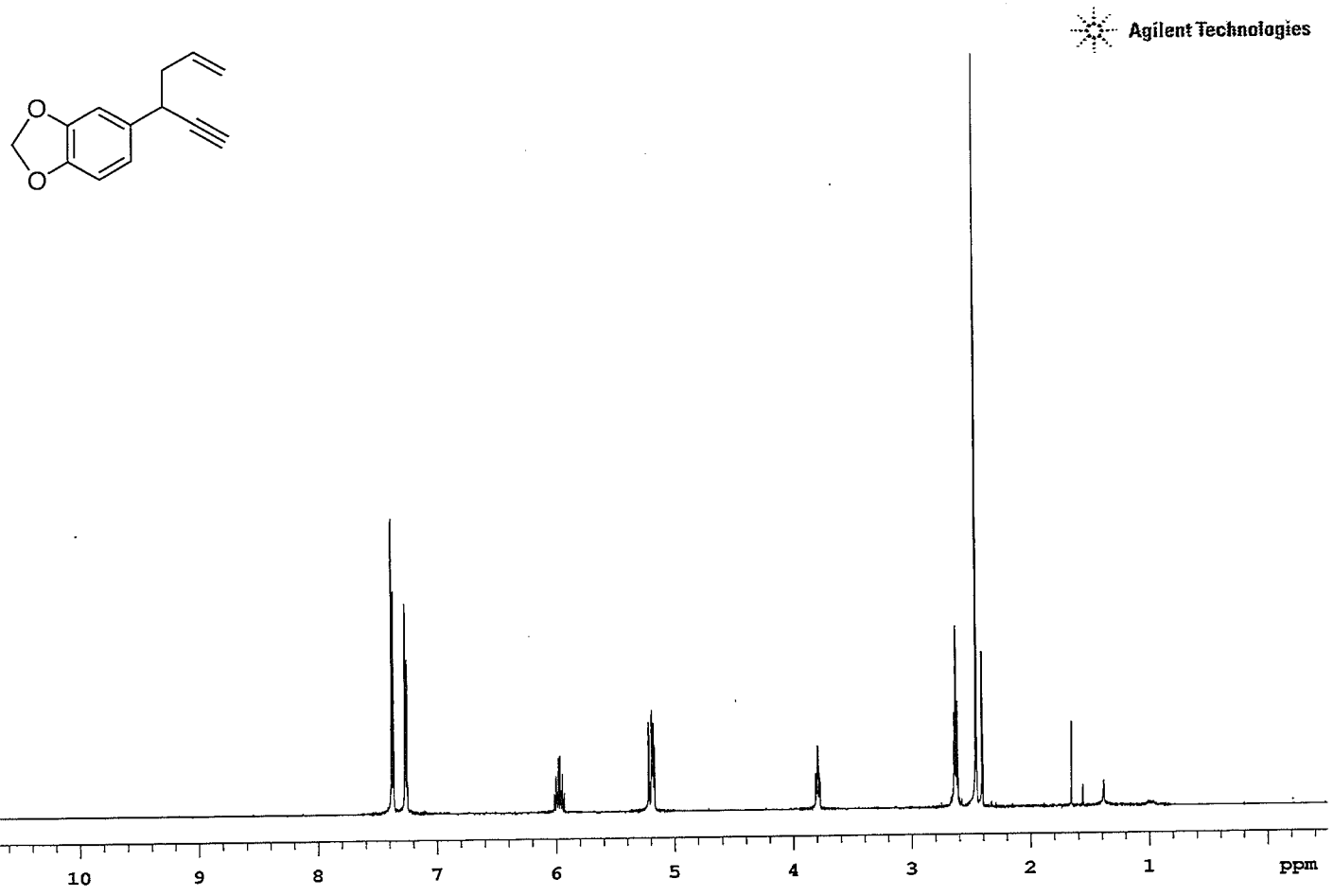
ppm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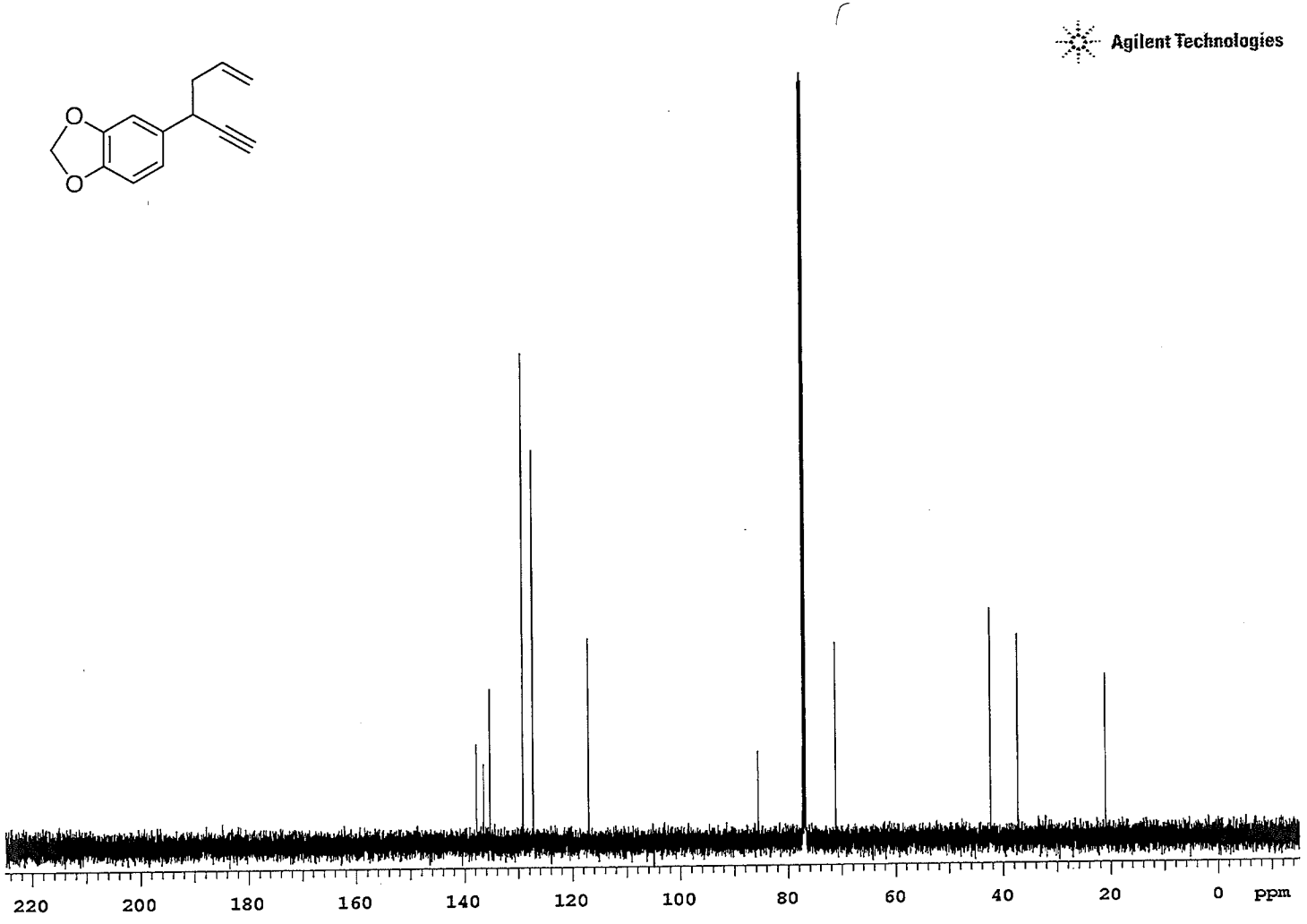
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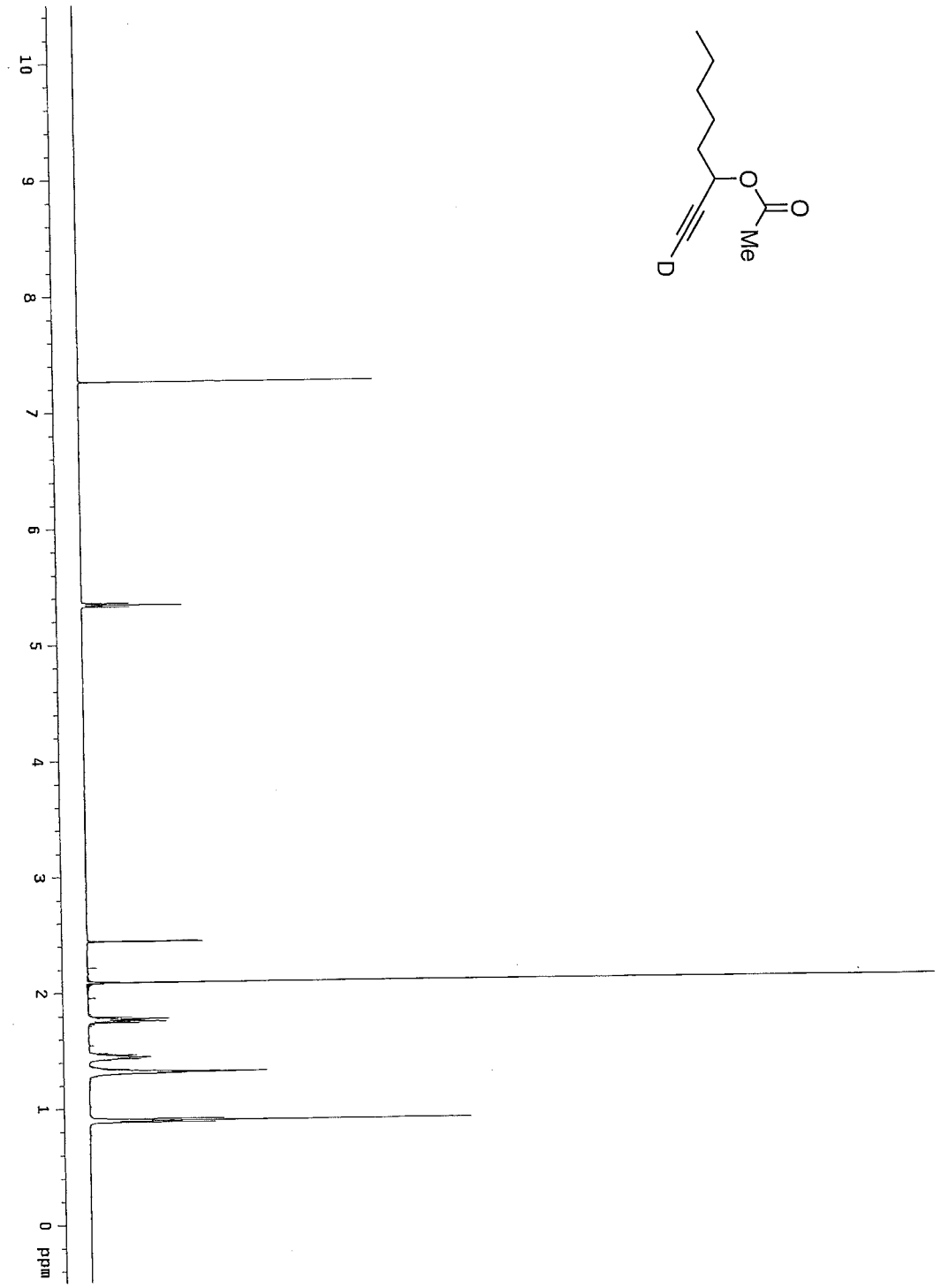
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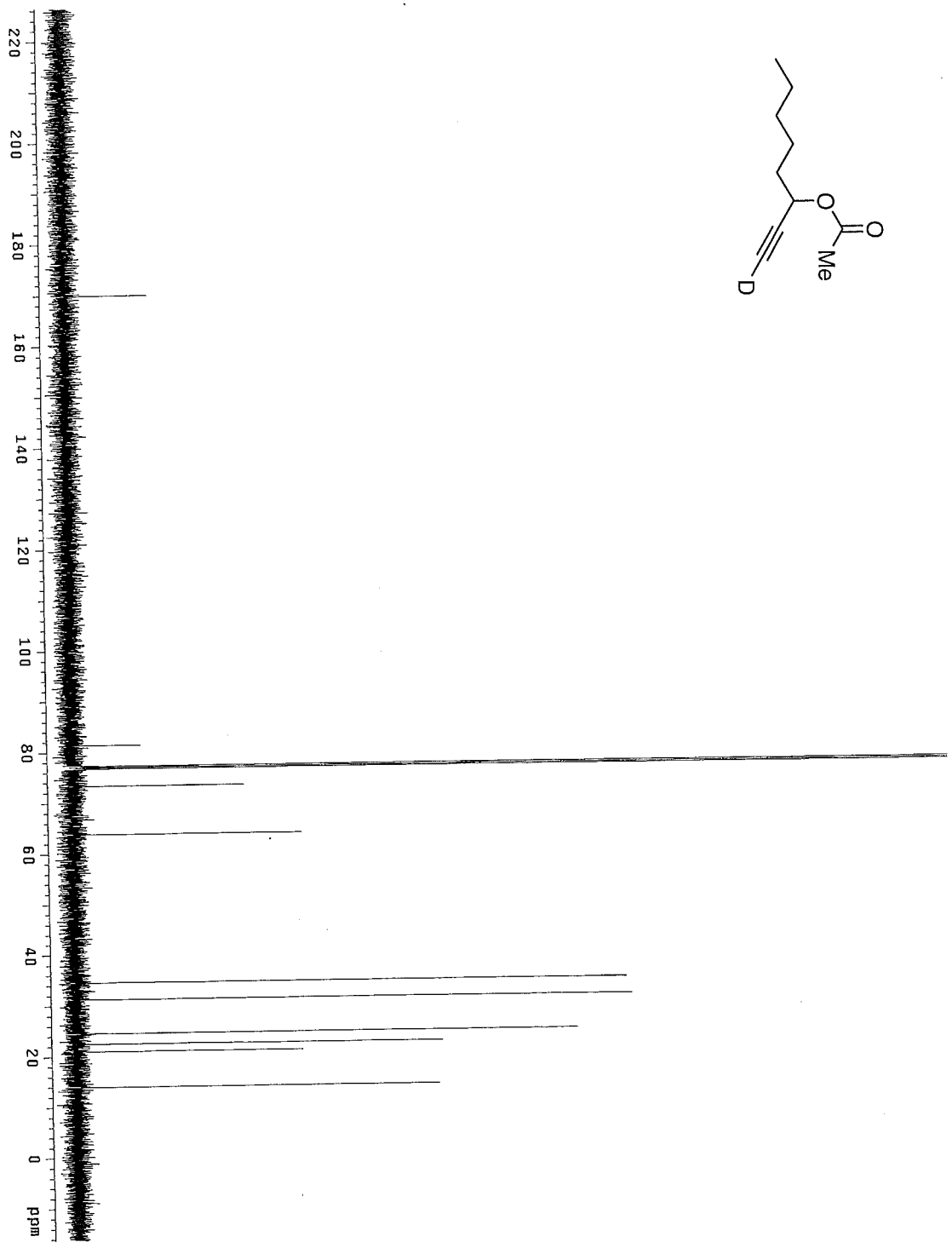
ppm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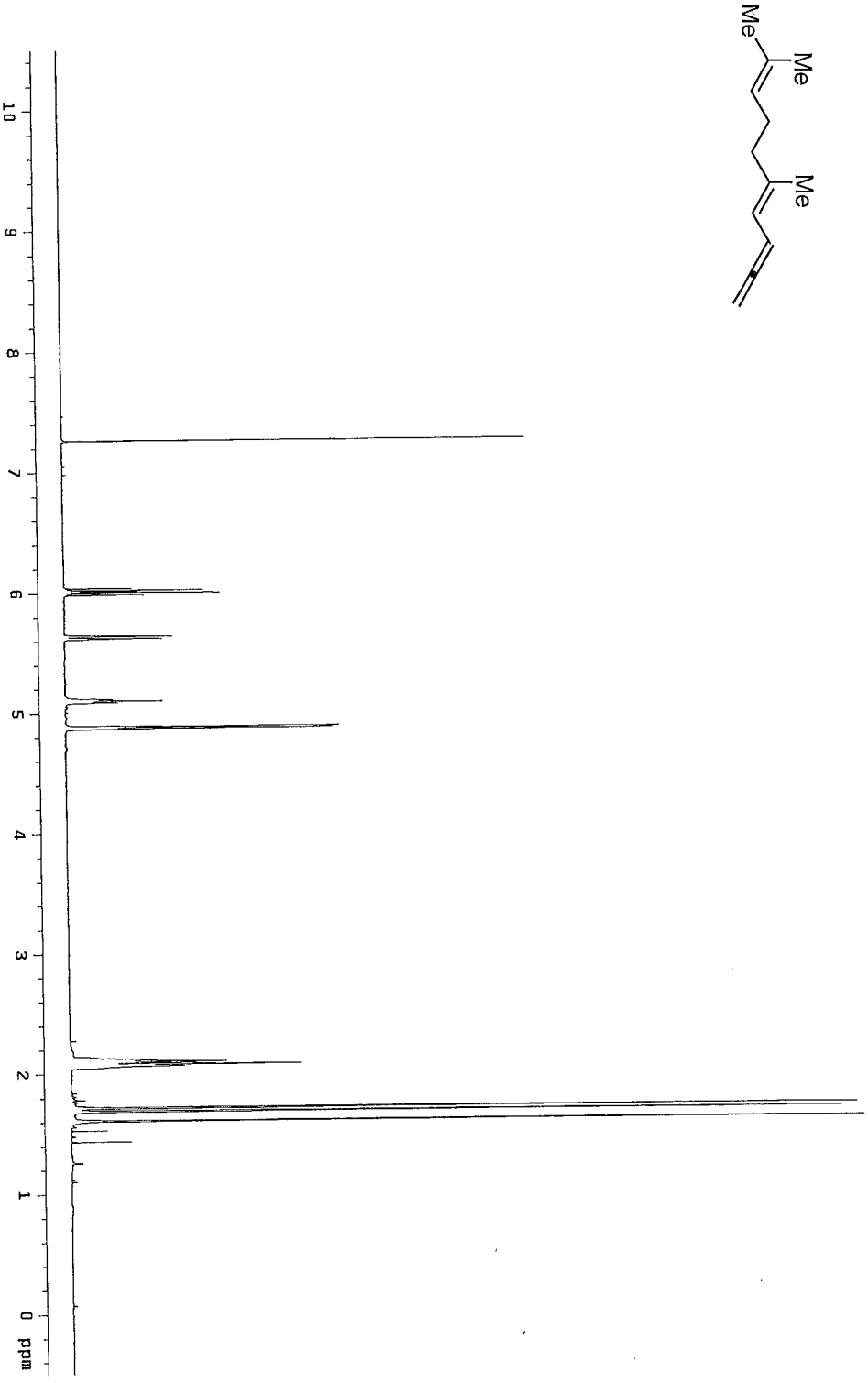
ppm
O
O
Me
D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1
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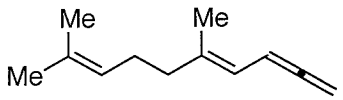
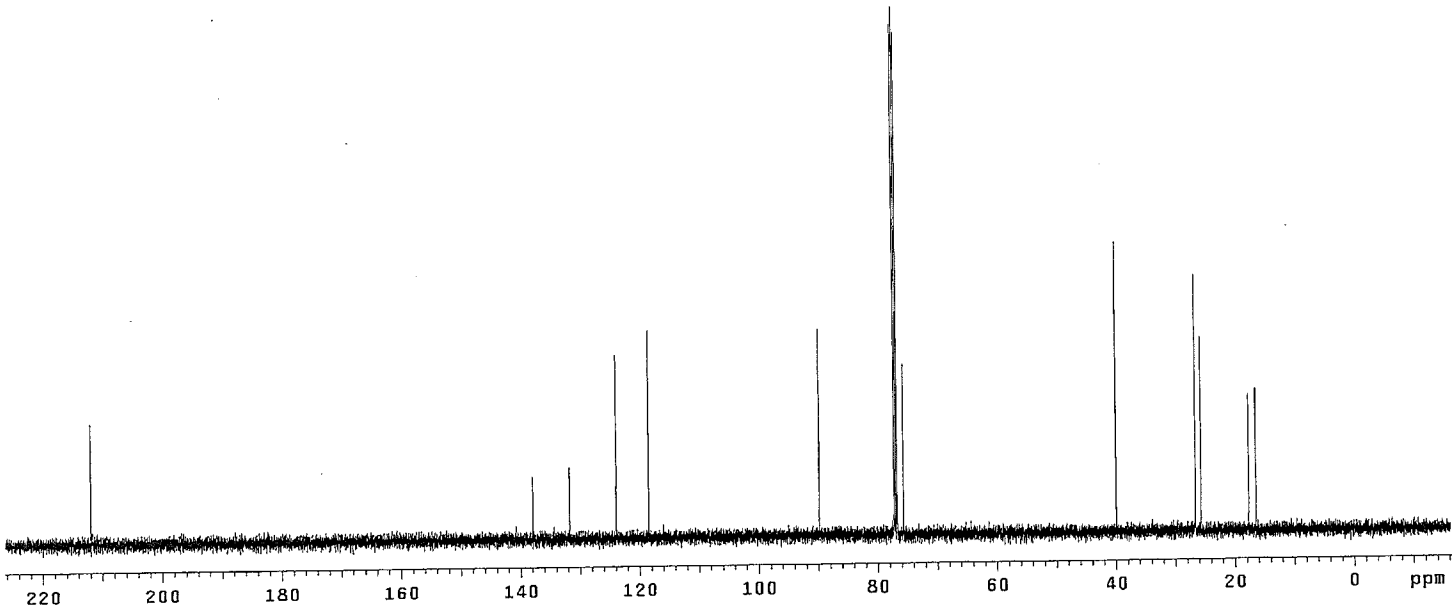
ppm


Me
Me
Me


220
200
180
160
140
120
100
80
60
40
20
0
ppm

# Chapter 2

## Enantioselective Hydroformylation of Unactivated Terminal Olefins with a Simple Bidentate Phosphine Ligand

## 2.1 Introduction

Asymmetric hydroformylation (AHF) has recently gained interest as an efficient and inexpensive method of preparing $\alpha$-chiral aldehydes (Scheme 2.1). AHF is especially attractive from a synthetic standpoint due to the complexity generated in one step from simple olefins with perfect atom economy. While high levels of regioselectivity and enantioselectivity in AHF have been realized with styrene derivatives, dienes, vinyl acetates/amides and other electronically-biased alkenes, only recently have non-activated or lowly activated alkenes been examined. In this chapter, I will present the discovery and optimization of a highly enantioselective and regioselective asymmetric hydroformylation of terminal olefins.

## 2.2 Overview of Asymmetric Hydroformylation

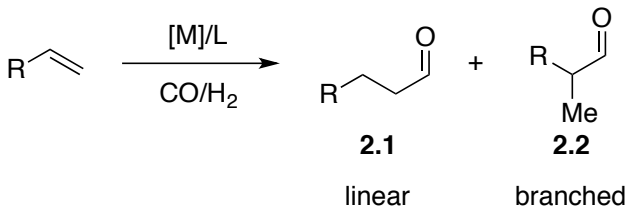
### *2.2.1 Discovery of Hydroformylation and Mechanism*

Since its discovery in the late 1930's, hydroformylation–also known as the oxo-process–has become one of the largest scale industrial processes.[1] Metal-catalyzed

[1] Claver, C.; Van Leeuwen, P. W. N. M. In *Rhodium Catalyzed Hydroformylation*; Claver, C.; Van Leeuwen, P. W. N. M., Eds.; Kluwer Academic Publisher: Norwell, MA, 2000; Vol. 22, pp 107-141, and references therein.

hydroformylation of terminal olefins give two regioisomeric products, an achiral linear aldehyde **2.1** and a chiral branched aldehyde **2.2** (Scheme 2.1).

**Scheme 2.1: Metal-Catalyzed Hydroformylation**




The achiral aldehydes **2.1** are used industrially to synthesize detergents and plasticizers. The chiral aldehyde **2.2** is a useful material as well, and can be easily used in the synthesis of active pharmaceutical ingredients. Linear-selective hydroformylation has been investigated extensively and is used on industrial scale, producing over 10 million tons of aldehyde annually.[2] Asymmetric hydroformylation to access the branched isomer is much less developed and to date has not been run on an industrial scale.[2a]

There are several challenges facing the development of a scalable AHF: (a) chemoselectivity: achieving hydroformylation without alkene isomerization or hydrogenation; (b) regioselectivity: high branched-versus-linear selectivities; and (c) enantioselectivity: high temperatures are usually required for HF and controlling

[2] (a) Chen, C.; Dong, X.-Q.; Zhang, X. *Chem. Rev.* **2016**, *16*, 2674. (b) Landis, C. R.; Klosin, J. *Accs. Chem. Res.* **2007**, *40*, 1251. (c) Claver, C.; Van Leeuwen, P. W. N. M. In *Rhodium Catalyzed Hydroformylation*; Claver, C.; Van Leeuwen, P. W. N. M., Eds.; Kluwer Academic Publisher: Norwell, MA, 2000; Vol. 22, pp 107-141.

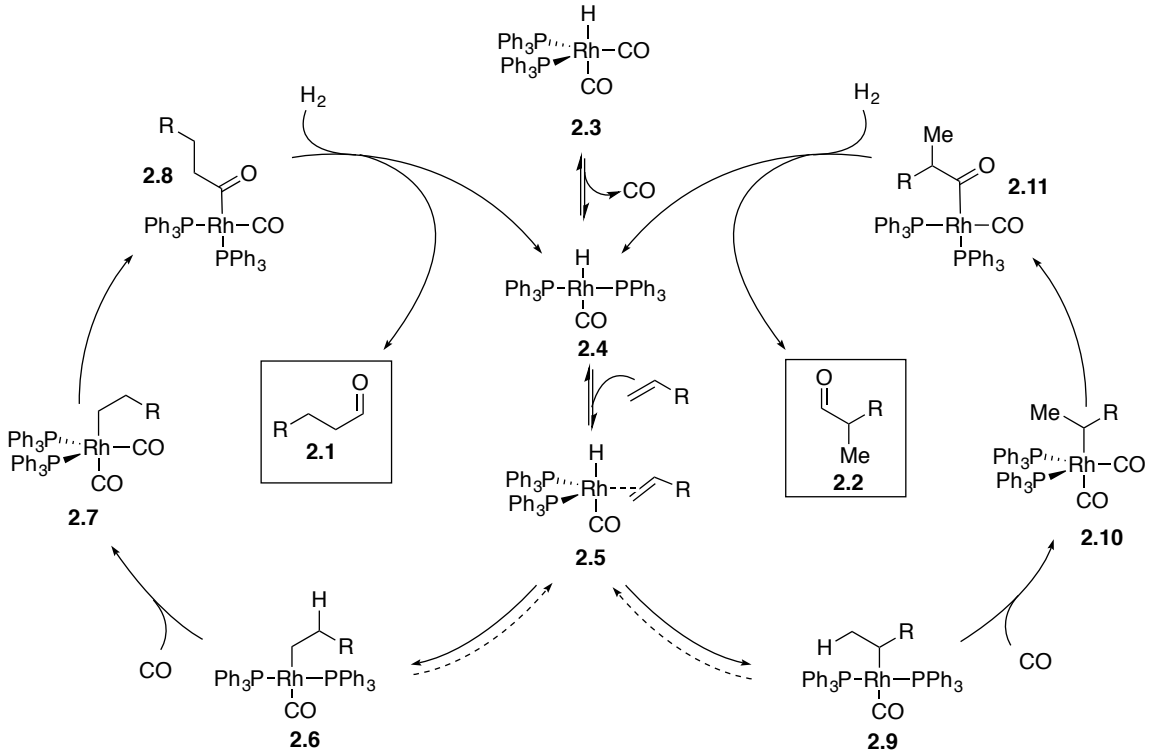
enantioselectivity at high temperature can be challenging. In addition to this, certain α-chiral aldehydes can racemize at elevated temperatures.[3]

The mechanism of rhodium-catalyzed hydroformylation has been extensively studied and is known to begin with 18 $e^-$ rhodium hydride **2.3** (Scheme 2.2).[4] The first step to enter the cycle requires CO dissociation, which is usually slow and requires elevated temperatures. After dissociation of CO to give **2.4**, coordination of the alkene yields **2.5**. At this point migratory insertion occurs; the rhodium can bond to the terminal carbon giving **2.6** or the internal carbon giving **2.9**. Association of CO to the 4-coordinate complex, followed by insertion to the alkyl chain results in a Rh-acyl complex (**2.8** or **2.11**). Hydrogenolysis of **2.8** or **2.11** releases the product and regenerates the rhodium hydride **2.3**.

[3] (a) Watkins, A. L.; Hashiguchi, B. G.; Landis, C. R.; *Org. Lett.* **2008**, *10*, 4553. (b) Axtell, A. T.; Klosin, J.; Abboud, K. A. *Organometallics* **2006**, *25*, 5003. (c) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251.

[4] (a) Jardine, F. H. *Polyhedron* **1982**, *1*, 569. (b) Csontos, G.; Heil, B.; Marko, L. Ann. N. Y. *Acad. Sci*. **1974**, *239*, 47. (c) Heck, R. F.; Breslow, D. S. *J. Am. Chem. Soc*. **1961**, *83*, 4023. (d) Claver, C.; Van Leeuwen, P. W. N. M. In *Rhodium Catalyzed Hydroformylation*; Claver, C.; Van Leeuwen, P. W. N. M., Eds.; Kluwer Academic Publisher: Norwell, MA, 2000; Vol. 22, pp 107-141.

**Scheme 2.2: Proposed Mechanism of Rhodium-Catalyzed Hydroformylation**




The hydrometallation step of the cycle determines the regio- and enantioselectivity of the reaction and is usually irreversible.[5] Typically, insertion of the rhodium to the terminal carbon of the olefin is favored (**2.6**), since it reduces steric interactions between the alkyl chain and ligand. There are two major ways of influencing the insertion of the rhodium to the olefin to favor **2.9**, the first of which is substrate choice. There are several examples of overriding linear selectivity with the addition of directing groups on the substrate.[6] Outside of the use of directing groups, electron-deficient alkenes such as

[5] Breit, B.; Seiche, W. *Synthesis* **2001**, 1.

[6] (a) Worthy, A.D.; Joe, C.L.; Lightburn, T.E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757. (b) Grunanger, C.U.; Breit, B. *Angew. Chem. Int. Ed*. **2008**, *47*, 7346. (c) Krafft, M. E.; Wilson, L. J.; Onan, K. D. *Tetrahedron Lett.* **1989**, *29*, 642. (d) Krafft, M. E.; Yu, X. Y.; Milczanowski, S. E.; Donnelly, K. D. *J. Am. Chem. Soc.* **1992**, *114*, 9215.

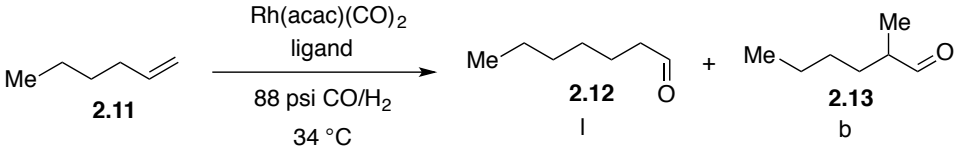
vinyl acetate, allyl cyanide and styrene will favor insertion to **2.9**. This is due to the higher stability of the metal-carbon bond formed in **2.9** (versus **2.6**) due to increased stabilization of the formal negative charge developing at the carbon by the electron-withdrawing group.[7]

Though certain substrates have an inherent steric or electronic preference to form one isomer over the other, specialized chiral ligand structures can overturn the regioselectivity in the hydroformylation. Casey and Whitaker have investigated how the natural bite angles of bidentate phosphine ligands correlate with the regioselectivity of Rh-catalyzed hydroformylation.[8] They determined that bidentate ligands with wider bite angles will favor formation of the linear isomer in the hydroformylation of 1-hexene (Table 2.1). The only exception is norbornyl ligand **L2.5**, which is proposed to act as a monodentate ligand. The authors could never isolate monomeric **L2.5**-Rh complex to support this hypothesis.[8a]

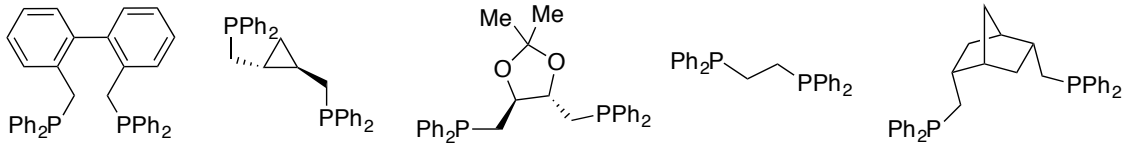
[7] Ojima, I. *Chem. Rev.* **1988**, *88*, 1011.

[8] (a) Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavey, J. A.; Powell, D. R. *J. Am. Chem. Soc.* **1992**, *114*, 5535. (b) Casey, C. P.; Whiteker, G. T. *Isr. J. Chem*. **1990**, *30*, 299. (c) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741.

**Table 2.1: Correlation of Bidentate Phosphine Natural Bite-Angle and Regioselectivity in HF.**



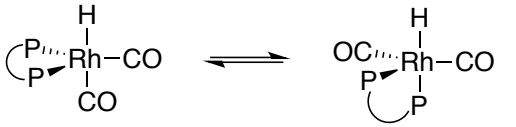

| diphosphine | turnover rate | l:b | calculated Rh(diphosphine) bite angle |
|---|---|---|---|
| **L2.1** | 29.4 | 66.5:1 | 112.6 |
| **L2.2** | 3.7 | 12.1:1 | 106.6 |
| **L2.3** | 6.4 | 8.5 | 102.2 |
| **L2.4** | 1.1 | 2.1:1 | 84.5 |
| **L2.5** | 9.3 | 2.9:1 | 126.1 |




**L2.1** **L2.2** **L2.3** **L2.4** **L2.5**

Through the use of IR and NMR spectra of HRh(diphosphine)CO complexes it was determined that wider bite angle diphosphines will favor ligand binding in the equatorial-equatorial sites (**2.14**, Scheme 2.3). Ligands with bite angles closer to 90 ° have significantly more of the equatorial-axial isomer (**2.15**, Scheme 2.3). Increasing the steric bulk around the rhodium center in **2.14** isomer, will result in more selective formation of the less hindered rhodium species **2.6**, leading to the linear product (Scheme 2.2).

**Scheme 2.3: Binding of Bidentate Phosphine Ligands to Rhodium**




**2.14**
equatorial-equatorial
(ee)

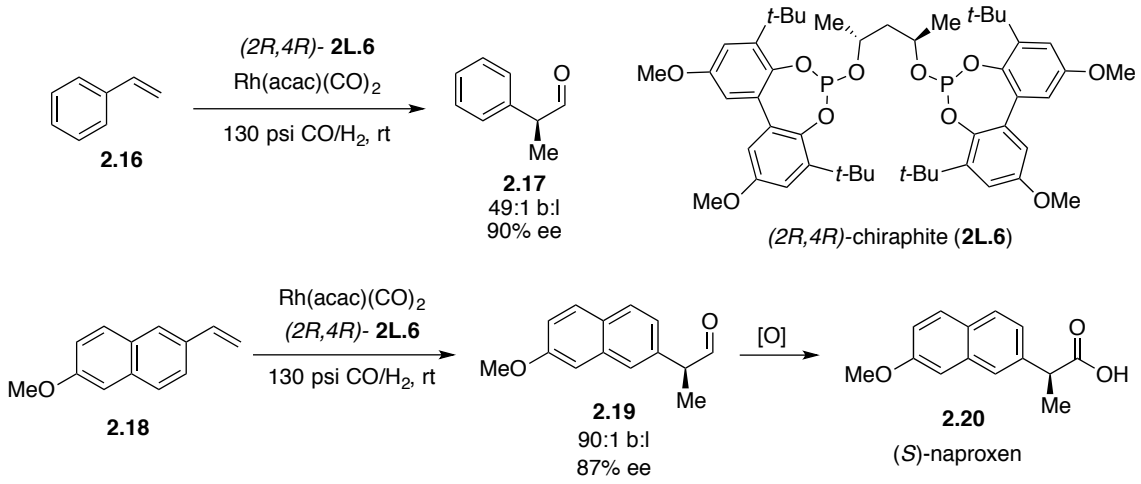
**2.15**
equatorial-axial
(ea)

### *2.2.2 Development of Specialized Ligands for Rh-cat AHF*

In 1992, chemists at Union Carbide presented *(2R, 4R)*-chiraphite (**L2.6**) as the first ligand scaffold able to deliver high regio- and enantioselective AHF of styrenes (Scheme 2.4).[9] This research group was also able to streamline the synthesis of the nonsteroidal anti-inflammatory drug Naproxen using this method.[10] Though high enantio- and regioselecivities are possible with **L2.6**, low activities are observed and at elevated temperatures the asymmetric induction is diminished.

[9] Whiteker, G. T.; Briggs, J. R.; Babin, J. E.; Barner, B. A. In *Catalysis of Organic Reactions*; Morrell, D. G., Ed.; Marcel Dekker: New York, 2003; p 359.
[10] Babin, J. E.; Whiteker, G. T.m inventors. Union Carbide Chemical & Plastics Technology Corp., assignee. Asymmetric Syntheses. WO 9303839, 1993, Mar 4.

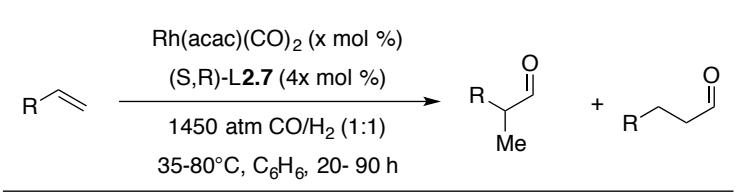
**Scheme 2.4: Rhodium-Catalyzed AHF with (2*R, 4R*)-Chiraphite and Synthetic Utility.**

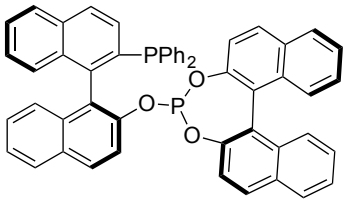



In 1997, Nozaki *et al.* developed the mixed phosphine-phosphite ligand binaphos **L2.7**. Binaphos is an excellent ligand for the AHF of several alkenes, observing high enantioselectivities and moderate-to-good regioselectivities (Table 2.2).[11] The hybrid ligand offers control of the ligand coordination to the metal. Due to the difference in electronic properties of the two phosphine atoms, it has been determined that only the ea coordination is possible with **L2.7** (Scheme 2.3), with the phosphine in the equatorial position and phosphite in the axial.[12] Though this ligand offers some advantages over **L2.6**, the scope is still limited. For instance, AHF of 1–hexene with **L2.7** results in the linear isomer as the major product.

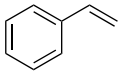
[11] Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc*. **1993**, *115*, 7033.
[12] Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413.

**Table 2.2: Rhodium-Catalyzed AHF with (*S, R*)-Binaphos.**

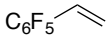


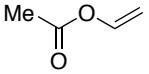

*(S, R)*-binaphos (**L2.7**)



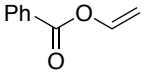
**2.16**
94% ee
7.3:1



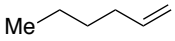

**2.20**
96% ee
32:1




**2.21**
92% ee
6.1:1




**2.22**
89% ee
10.1:1




**2.11**
89% ee
1:3.2

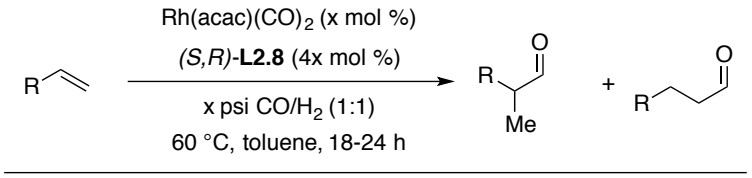
Since the development of hybrid ligand **L2.7** for rhodium catalyzed AHF, several other hybrid ligand scaffolds have been developed.[13] In 2010, Zhang and co-workers predicted that synthesis of a hybrid ligand with an N-substituted phosphoramidite in place of the phosphite in binaphos **L2.7** would lead to a more rigid chiral pocket and lead to higher enantioselectivites.[14] Their prediction was correct and YanPhos **L2.8** has been shown to give high yields, as well as enantio- and regioselectivities for a variety of substrate classes (Table 2.3).

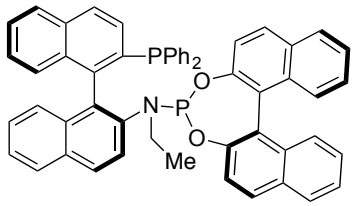
---

[13] (a) Schmitz, C.; Holthusen, K.; Leitner, W.; Francio, C. *ACS Catal.* **2016**, *6*, 1584. (b) Doro, F.; Reek, J. N. H.; van Leeuwen, P. W. N. M. *Organometallics*, **2010**, *29*, 4440. (c) Bonafoux, D.; Hua, Z.; Wang, B.; Ojima, I. *J. Fluorine. Chem.* **2001**, *112*, 101. (d) Deerenberg, S.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **2000**, *19, 2065.* (e) Ewalds, R.; Eggeling, E. B.; Hewat, A. C.; Kramer, P. C. J.; van Leeuwen, P. W. N. M.; Vogy, D. *Chem. Eur. J.* **2000,** *6*, 1496. Francio, G.; Faraone, F.; Leitner, W. *Angew. Chem. Int. Ed.,* **2000**, *39*, 1428.

[14] Chen, C.; Dong, Q.-X.; Zhang, X. *Chem. Rec.* **2016**, *16*, 2674.

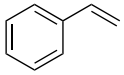
**Table 2.3: Rhodium-Catalyzed AHF with (*S, R*)-YanPhos.**



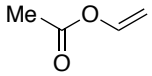




*(S, R)*-yanphos (**L2.8**)

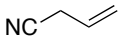
x = 290



**2.16**
94% ee
7.2:1

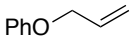



**2.21**
98% ee
14:1

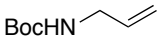



**2.23**
96% ee
4:1

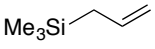
x = 72




**2.24**
94% ee
2.4:1




**2.25**
94% ee
2:1

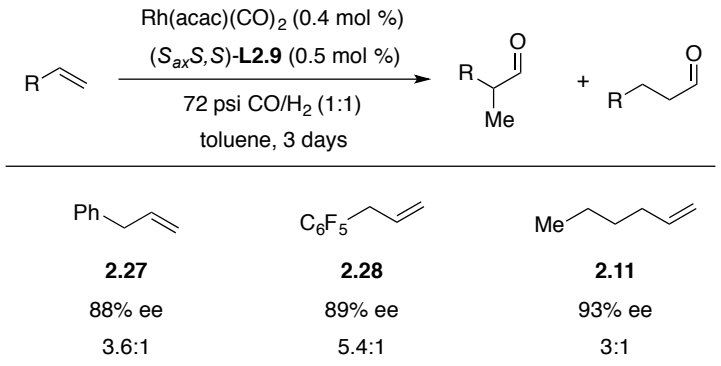



**2.26**
94% ee
2.6:1

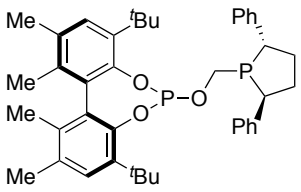
BobPhos **L2.9**, developed by Clarke and co-workers in 2012, is another hybrid ligand scaffold that has been shown to give high branched selectivities for nonelectronically-biased alkenes such as 1-hexene (Table 2.4).[15] This ligand, to date, gives the highest branched:linear ratio for aliphatic terminal olefins. However, in order to obtain these high selecitivies, the reaction needs to be run at 16 °C for 3 days, making this an unpractical method.

[15] Noonan, G. M.; Fuentes, J. A.; Colbey, C. J.; Clarke, M. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 2477.

**Table 2.4: Rhodium-Catalyzed AHF with BobPhos**




| **2.27** | **2.28** | **2.11** |
|---|---|---|
| 88% ee | 89% ee | 93% ee |
| 3.6:1 | 5.4:1 | 3:1 |

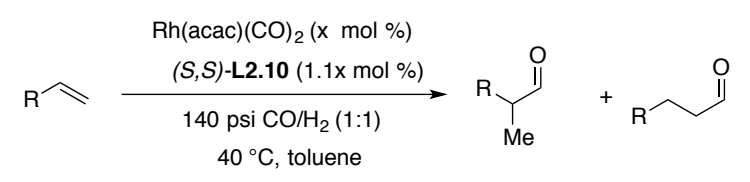



($S_{ax}S,S$)-BobPhos **(L2.9)**

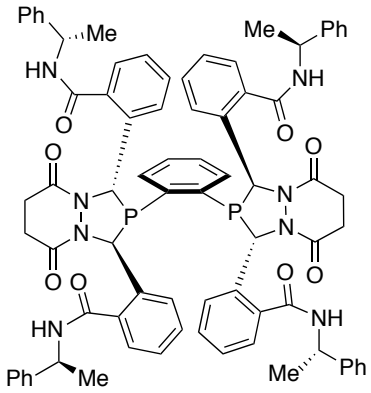
Bisdiazaphos ligands such as **L2.10**, are the benchmark ligands for the AHF of substrates outside of allyl cyanide, styrene, and vinyl acetate.[16] These ligands give high enantio- and regioselectivities with substrates such as allyl ethers and N-allyl amines while maintaining high activity and fast reaction times, even at decreased catalyst loadings (Table 2.5).

[16] (a) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040. (b) Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R.; Abboud, K. A. *Org. Lett*. **2007**, *9*, 2665. (c) Watkins, A. L.; Hashiguchi, B. G.; Landis, C. R. *Org. Lett.* **2008**, *10*, 4553. (d) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027.

**Table 2.5: Rhodium-Catalyzed AHF with (*S, S)-Bisdiazaphos***



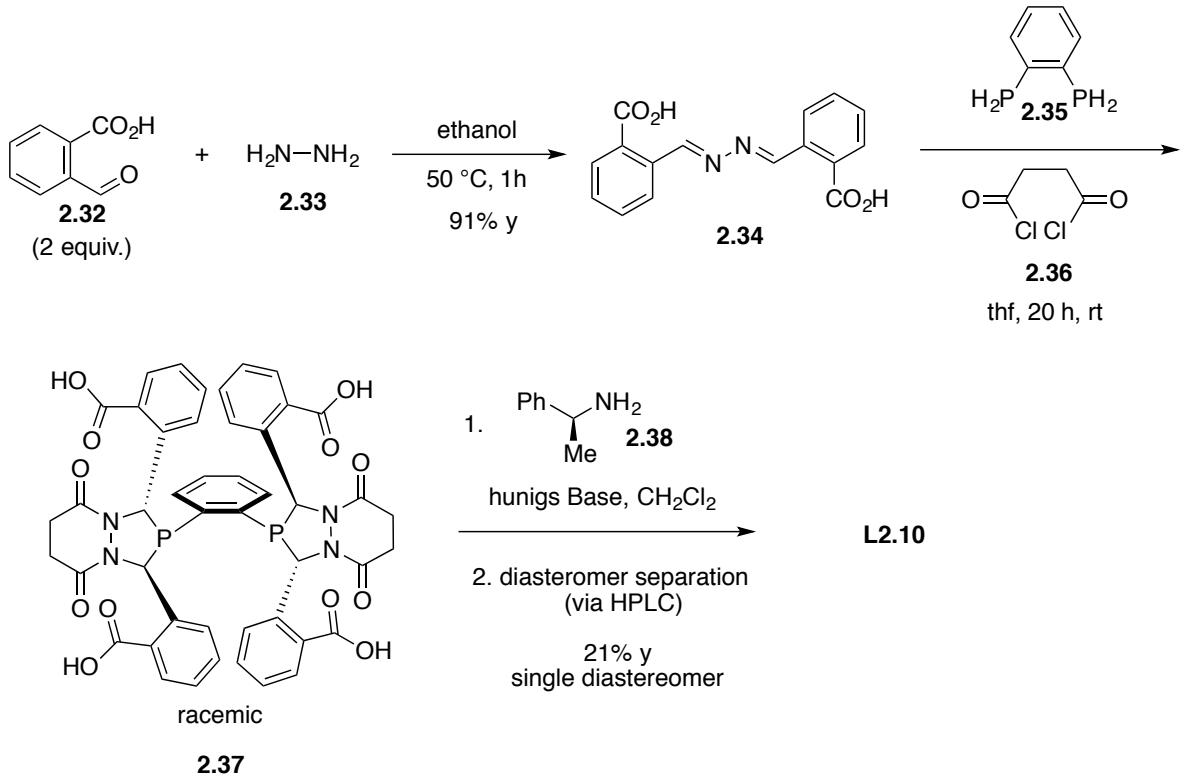

| PhO | TMSO | O, O |
|---|---|---|
| **2.29** | **2.30** | **2.31** |
| 88% ee | 97% ee | 92% ee |
| 3.6:1 | 2:1 | 4.2:1 |




*(S,S)*-bisdiazaphos (**L2.10**)

Developed by Landis in 2005, the only drawback is limited access to the bisdiazaphos ligand due to a tedious synthesis (Scheme 2.5).[16a] Condensation of arylaldehyde **2.32** with hydrazine **2.33** gives azine **2.34** in high yield. Cyclization of azine **2.34** with diphosphinobenzene **2.35** and bisacid chloride **2.36** results in racemic tetraacid **2.37** as one diastereomer. Condensation of the chiral amine **2.38** results in a mixture of two diastereomers, one of which is active. A difficult separation using chiral HPLC is necessary to give the desired single diastereomer **L2.10**. Another drawback is that only electron-withdrawing amide groups in the *ortho*-position can be introduced, limiting the tunablility of the scaffold.[14]

**Scheme 2.5: Synthesis of Bisdiazaphos Ligands**



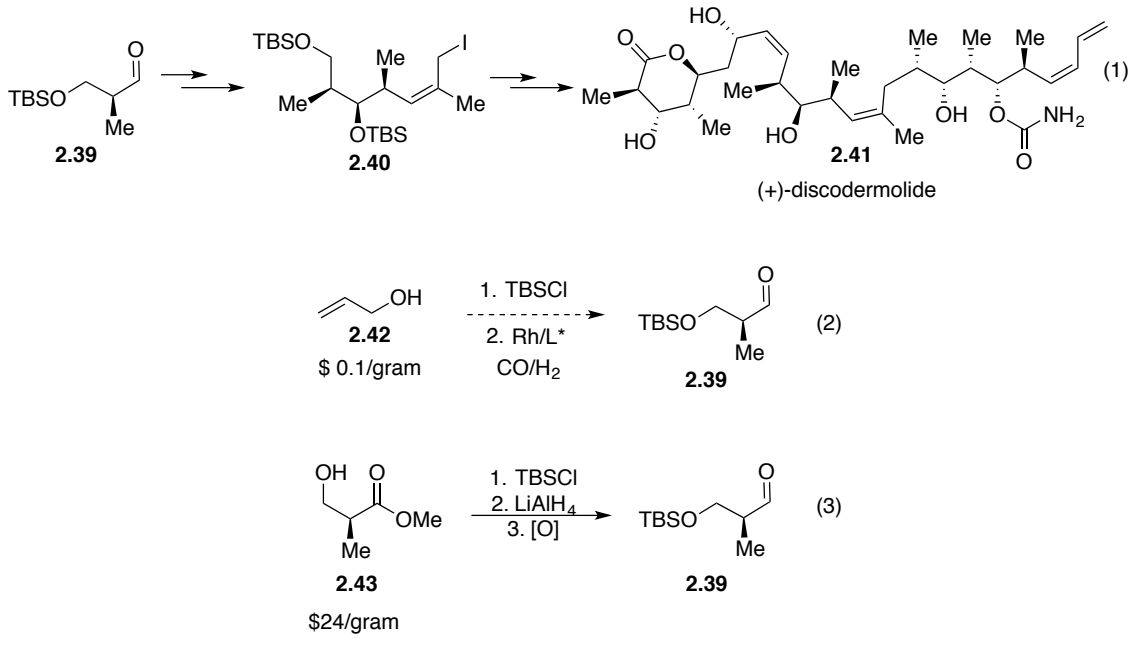

Though there are several ligand scaffolds that can give high regio- and enantioselectivities for electronically-biased substrates such as styrene, there are only a few ligands that can be used with substrates such as 1-hexene. In addition, the current bench mark ligands suffer from low activities or difficult syntheses. The development of other ligand scaffolds for the AHF of nonelectronically-biased olefins with broader substrate scopes is still necessary.

## 2.3 Development of Asymmetric Hydroformylation with Simple Bidentate Phosphines[17]

### *2.3.1 Application of AHF to Total Synthesis of (+)-Discodermolide and Initial Results*

Our interest in asymmetric hydroformylation started in the planning stages for the total synthesis of (+)-discodermolide **2.41**, in which AHF of allylic ethers would streamline the synthesis of key building block **2.40** (Scheme 2.6). If we could find a highly selective AHF, aldehyde **2.39** could be prepared in two-steps from allyl alcohol **2.42** (eq. 2). Aldehydes like **2.39** are typically prepared from comparably expensive Roche ester **2.43** in a number of synthetic steps (Scheme 2.6, eq. 3).

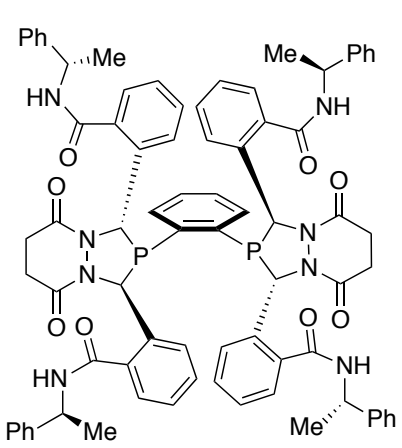
**Scheme 2.6: Streamlining the Synthesis of Disocdermolide with AHF**



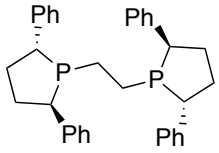

[17] Eno, M. S.*; Yu, Z.*; Annis, A. H. Morken, J. P. *Org. Lett.* **2015**, *17*, 3264.

The AHF of allyl alcohol derivatives with bisdiazaphos ligands has been presented by Landis and co-workers; however, this ligand is not readily available (*vide supra*).[18] We predicted that the bis(phospholano)ethane (BPE) and bis(phospholano)benzene (DuPhos) families of ligands could be used due to their similarities in structure and electronic nature to the bisdiazaphos ligands. In addition to their similarities in structures, many derivatives of these ligands are commercially available as single enantiomers (Scheme 2.7).[19]

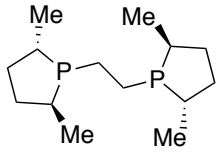
**Scheme 2.7: Comparison of Different Bidentate Phospholane Ligands**



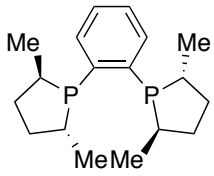
**L2.10**
*(S,S)*-bisdiazaphos



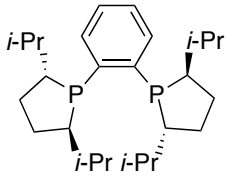
**L2.11**
*(S,S)*-PhBPE



**L2.12**
(*S.S*)-MeBPE



**L2.13**
(*R,R*)-MeDuphos



**L2.14**
(*S,S*)-*i*-PrDuPhos

[18] McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027.

[19] For example, 33 DuPhos and BPE ligands are available from Sigma-Aldrich, 14 from Strem Chemicals Inc. (data as of 12/12/2016).

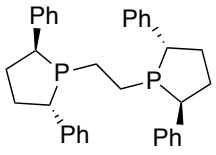
Bidentate BPE and DuPhos ligands have found extensive use as efficient and highly selective ligands in a broad range of asymmetric hydrogenation.[20] We are not the first group to recognize that BPE and DuPhos ligands could be efficient asymmetric hydroformylation catalysts. In 2005, Klosin and co-workers investigated a range of phospholane ligands in the AHF of styrene, allyl cyanide and vinyl acetate (Table 2.6).[21] Interestingly, in some cases, simple ligands such as PhBPE **L2.11** gave higher regio- and enantioselectivities than bisdiazaphos **L2.10**. However, the use of these ligands in the AHF of nonelectronically-biased alkenes such as 1-hexene has not been investigated.

[20] For a review on asymmetric reactions with phospholane ligands see: Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.
[21] Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 5834.

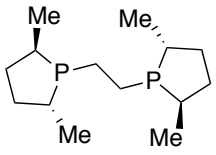
**Table 2.6: Investigation of Phospholane Ligands in AHF**

| | | styrene | | | allyl cyanide | | | vinyl acetate | | |
|---|---|---|---|---|---|---|---|---|---|---|
| entry | ligand | conv. | b/l | *ee* (%) | conv. | b/l | *ee* (%) | conv. | b/l | *ee* (%) |
| 1 | **L2.13** | 10 | 15.7:1 | 44 | 42 | 6.6:1 | 32 | 26 | 176:1 | 51 |
| 2 | **L2.14** | 15 | 11.3:1 | 83 | 55 | 7.2:1 | 82 | 29 | 322:1 | 74 |
| 3 | **L2.12** | 8 | 14:1 | 43 | 36 | 5.8:1 | 37 | 23 | 97:1 | 59 |
| 4 | **L2.11** | 57 | 45:1 | 94 | 96 | 7.1:1 | 90 | 52 | 340:1 | 82 |
| 5 | **L2.10** | 100 | 6.6:1 | 82 | 100 | 4.1:1 | 87 | 100 | 37:1 | 96 |

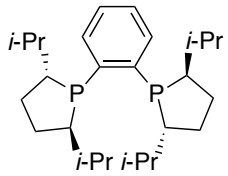
All the reactions were performed at 80 °C in toluene with 150 psi $CO/H_2$ (1:1), substrate/$Rh(acac)(CO)_2$ = 5000:1, catalyst concentration of 0.037% and a 3 h reaction time.



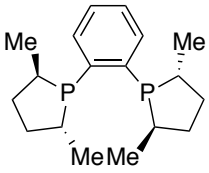

**L2.11**
*(R,R)*-PhBPE




**L2.12**
(*R,R*)-MeBPE




**L2.14**
(*S,S*)-*i*-PrDuPhos



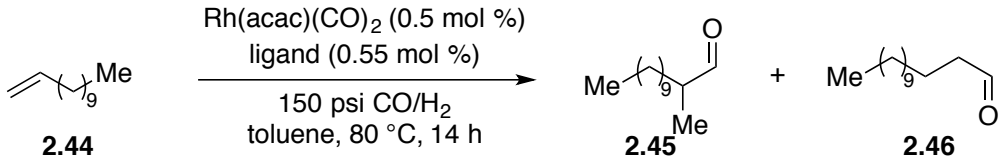

**L2.13**
(*R,R*)-MeDuphos

We began our investigation into the AHF of 1-alkenes using 1-dodecene **2.44** as our model substrate. Because of its high boiling point, it would be possible to observe any undesired hydrogenation byproducts. Since 1-alkenes are known to favor the linear isomer with a variety of ligand scaffolds,[22] high enantioselectivies and even modest branched selectivity would be encouraging enough to investigate other substrates. We were pleased to see that Rh-catalyzed AHF of 1-dodecene in toluene at 80 °C with *(S,S)*-PhBPE **L2.11**, gave a 1.2:1 branched-to-linear ratio with 95:5 er (Table 2.7). It was evident that having a large group on the cyclopentane ring was crucial for high enantioselectivities

[22] (a) Agbossou, F.; Carpentier, J.-F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485. (b) Cuny, G. D.; Buchwald, S. L. *J. Am. Chem. Soc*. **1993,** *115,* 2066.

(entry 1 vs. entries 2, 3). Since **L2.11** gave the highest regio- and enantioselectivities in this initial ligand screen, remainder of the optimization was performed with this ligand.

**Table 2.7: Initial Results for AHF of 1-dodecene with Phospholane Ligands**




**2.44** **2.45** **2.46**

| entry | ligand | **2.45:2.46**[a] | er **2.45**[b] |
|---|---|---|---|
| 1 | *(S,S)*-PhBPE **L2.11** | 1.2:1 | 5:95 |
| 2 | *(S,S)*-MeBPE **L2.12** | 0.9:1 | 55:45 |
| 3 | *(R,R)*-MeDuPhos **L2.13** | 0.5:1 | 41:59 |
| 4 | *(S,S)-i*-PrDuPhos **L2.14** | 1.1:1 | 93:7 |

a) ratio of products determined by $^1$HNMR analysis. b) enantomer ratios dertermined by SFC analysis on chiral stationary phase after reduction and benzoylation

### *2.3.2 Optimization of AHF of 1-Alkenes with (S,S)-PhBPE*

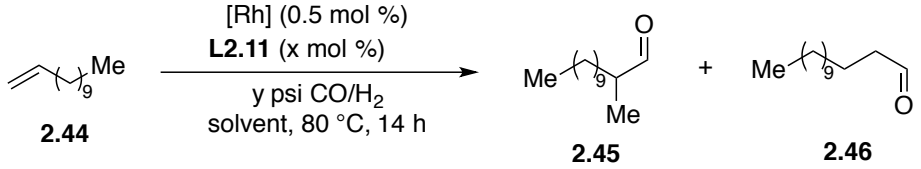
We were interested in further enhancing the regioselectivity of the reaction and predicted that perhaps other precatalysts, pressures, or solvents could improve the results (Table 2.8). Other rhodium precatalysts such as $[Rh(NBD)Cl]_2$ and $[RhCl(C_2H_4)_2]_2$ performed similarly to $Rh(acac)(CO)_2$. However, due to the higher cost of these other

precatalysts, $Rh(acac)(CO)_2$ continued to be used as the precatalyst.[23] Increasing the ligand-to-metal ratio did not affect the branched to linear ratio (entries 5, 6). Changes in the pressure of $CO/H_2$ (1:1) in the reaction also did not lead to significant changes in the regioselectivity (entries 7, 8). We did not investigate changing the $CO/H_2$ ratio, though Landis has shown that increase CO pressure independently of $H_2$ can lead to higher selectivities.[24] Changing the solvent in the reaction seemed to have the largest effect as acetonitrile led to diminished regio- and enantioselectivities, while thf gave similar results to toluene (entries 1, 9, 10). The higher enantioselectivity and regioselectivity in the reaction performed with thf is likely due to the decreased temperature.

[23] $Rh(acac)(CO)_2$ ($212/g), $[RhCl(C_2H_4)_2]_2$ ($574/g), $[Rh(nbd)Cl]_2$ ($357/1g) ; Aldrich (12/12/2016)

[24] Watkins, A. L.; Landis, C. R. *J. Am. Chem. Soc.* **2010***, 132*, 10306.

**Table 2.8: Optimization of AHF of 1-Dodecene with *(S,S)*-PhBPE**



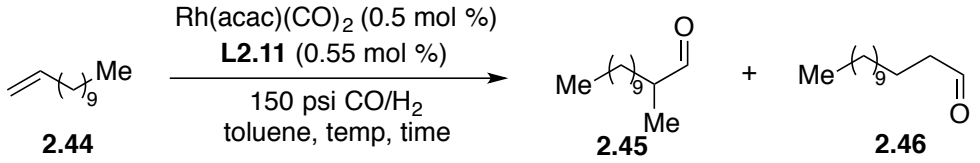

**2.44** **2.45** **2.46**

| entry | [Rh] | x % | solvent | y (psi) | **2.45:2.46**[a] (% *ee*)[b] |
|---|---|---|---|---|---|
| 1 | $Rh(acac)(CO)_2$ | 0.55 | toluene | 150 | 1.18:1 (90 %) |
| 2 | $[Rh(nbd)Cl]_2$ | 0.55 | toluene | 150 | 1.22:1 |
| 3 | $[RhCl(C_2H_4)_2]_2$ | 0.55 | toluene | 150 | 1.15:1 |
| 4 | $[Rh(OMe)COD]_2$ | 0.55 | toluene | 150 | 0.59:1[c] |
| 5 | $Rh(acac)(CO)_2$ | 1.0 | toluene | 150 | 1.17:1 |
| 6 | $Rh(acac)(CO)_2$ | 2.0 | toluene | 150 | 1.18:1 |
| 7 | $Rh(acac)(CO)_2$ | 0.55 | toluene | 75 | 1.11:1 |
| 8 | $Rh(acac)(CO)_2$ | 0.55 | toluene | 300 | 1.20:1 |
| 9 | $Rh(acac)(CO)_2$ | 0.55 | MeCN | 150 | 0.62:1 (22 %) |
| 10[c] | $Rh(acac)(CO)_2$ | 0.55 | thf | 150 | 1.4:1 (93 %) |

a) ratio of products determined by $^1$HNMR analysis. b) enantomer ratios dertermined by SFC analysis on chiral stationary phase after reduction and benzoylation . c) reaction performed at 60 °C.

Indeed, decreasing the temperature of the reaction in toluene, led to increased regio- and enantioselectivities up to 97% ee and 1.4:1 branched:linear ratio at 40 °C (Table 2.9). Though lower temperatures improved selectivities, the significant reaction times that would be required to obtain high conversions makes these conditions non-ideal. The reaction at 80 °C offers a nice balance of reaction rate and selectivity. With our ideal conditions in hand, we were excited to look at other terminal olefins.

**Table 2.9: Screening Different Temperatures for AHF with PhBPE**




| entry | temp. | time (h) | conv. | **2.45:2.46**[a] | er **2.45**[b] |
|---|---|---|---|---|---|
| 1 | 80 °C | 16 | 100% | 1.18:1 | 91% |
| 2 | 60 °C | 16 | 81% | 1.3:1 | 94% |
| 3 | 40 °C | 36 | 57% | 1.42:1 | 97% |
| 4 | 25 °C | 36 | n.r | n.d. | n.d. |

a) ratio of products determined by $^1$H-NMR analysis. b) enantomeric ratios dertermined by SFC analysis on chiral stationary phase after converting to benzoate protected alcohol.

### *2.3.3 Expanding the Socpe of AHF of 1-Alkenes with PhBPE*

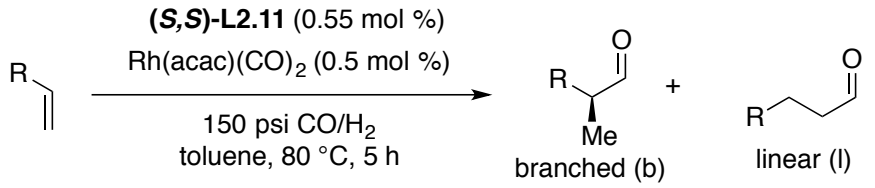
We were initially interested in looking at minimally electronically-biased substrates like TBS-protected allyl alcohol **2.47**, to give the β-siloxyl aldehyde **2.39** needed for the synthesis of (+)-discodermolide (*vide supra*) (Table 2.10). With our optimized conditions in hand we were pleased to see that aldehyde **2.39** was formed with 4:1 branched:linear ratio and high enantioselectivity. This result surpasses the 2:1 branched:linear ratio previously obtained with bisdiazaphos ligand **L2.10**.[25] Allyl ether **2.48** led to further enhanced regioselectivity and high enantioselectivity. Changing the

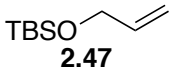
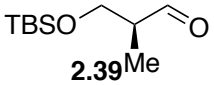
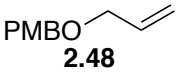
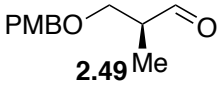
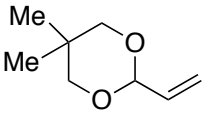
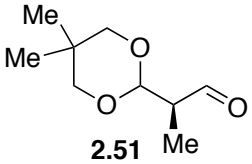
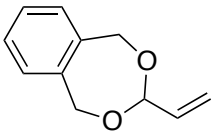
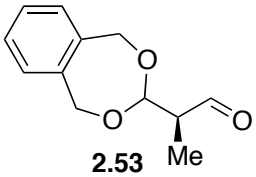
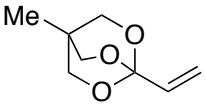
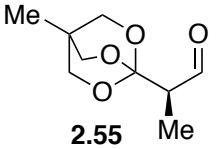
[25] Landis, C. R.; Nelson, R. C.; Jin, W.; Bowman, A. C. *Organometallics* **2006**, *25*, 1377.

oxidation state at the allylic position led to significantly improved regioselectivities with vinyl orthoester **2.54** giving a 15:1 branched:linear ratio and 96:4 er for **2.55**. Note that aldehyde **2.55** is also an important synthetic intermediate that has been previously used in the synthesis of Prelog-Djerassi lactone.[26]

[26] Ho, S.; Bucher, C.; Leighton, J. L. *Angew. Chem., Int. Ed*. **2013**, *52*, 6757.

**Table 2.10: AHF of Allylic Ethers and Vinyl Acetals with PhBPE**



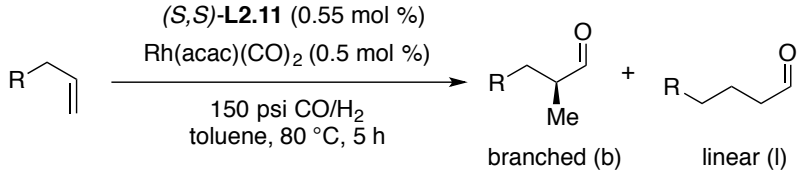

| entry | substrate | product | yield (%) | b:l [a] | er[b] |
|---|---|---|---|---|---|
| 1 |  **2.47** |  **2.39** | 72 | 3.9:1 | 98:2 |
| 2 |  **2.48** |  **2.49** | 78 | 5.5:1 | 96:4 |
| 3 |  **2.50** |  **2.51** | 91 | 12:1 | 96:4 |
| 4 |  **2.52** |  **2.53** | 90 | 10:1 | 96:4 |
| 5 |  **2.54** |  **2.55** | 91 | 15:1 | 94:6 |

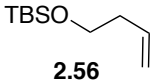
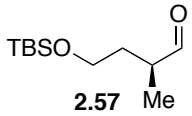
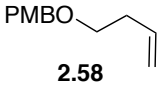
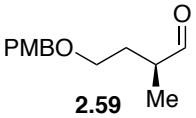
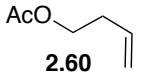
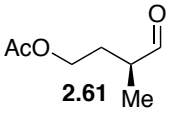
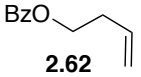
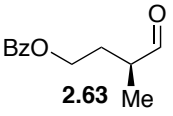
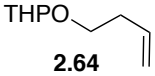
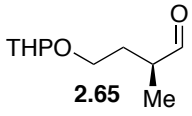
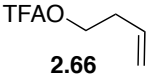
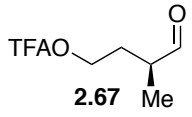
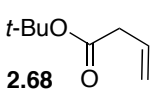
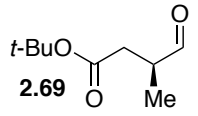
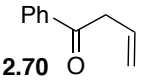
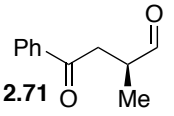
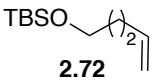
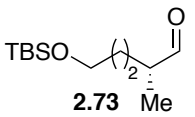
Reactions performed with 0.5 mol % $Rh(acac)(CO)_2$ and 0.55 mol % of (*S,S)*-**L2.11**; [substrate]=1.0M. [a]Branch:linear ration determined by $^1$H-NMR analysis. [b]enantomeric ratios dertermined by SFC analysis on chiral stationary phase.

Due to the success of PhBPE in the AHF of the above allyl ether and acetal derivatives, we wanted to further investigate substrates that are even less electronically-biased to give the branched isomer (Table 2.11). AHF of protected homoallylic alcohols

gave high enantioselectivities and moderate branched:linear ratios (entries 1- 6). Increasing the electron-withdrawing nature of the protecting group leads to higher regioselectivities **2.60**<**2.62**<**2.66** (entries 3, 4, 6). Again, increasing the oxidation state at the homoallylic position led to higher branched selectivities while the enantioselectivity remained high (entry 7, 8). Bishomoallylic silyloxy alkene **2.72** gave 1.2:1 branched:linear ratio with excellent enantioselectivity similar to that of 1-dodecene, indicating that the oxygen in this case has little electronic influence on the alkene and outcome of the reaction.

**Table 2.11: AHF of Nonelectronically Biased Alkenes with PhBPE**

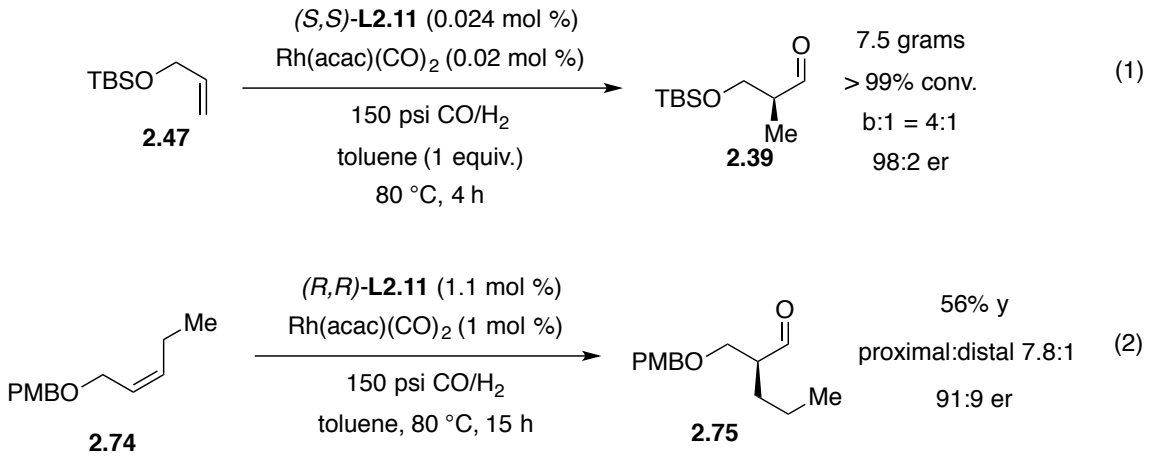



| entry | substrate | product | yield (%) | b:l [a] | er[b] |
|---|---|---|---|---|---|
| 1 |  **2.56** |  **2.57** | 65 | 2.2:1 | 97:3 |
| 2 |  **2.58** |  **2.59** | 60 | 2.3:1 | 95:5 |
| 3 |  **2.60** |  **2.61** | 62 | 2.2:1 | 95:5 |
| 4 |  **2.62** |  **2.63** | 69 | 2.6:1 | 96:4 |
| 5 |  **2.64** |  **2.65** | 37 | 2:1 | 88:13 |
| 6 |  **2.66** |  **2.67** | 63 | 3:1 | nd |
| 7 |  **2.68** |  **2.69** | 54 | 5.5:1 | 95:5 |
| 8 |  **2.70** |  **2.71** | 66 | 5.2 | nd |
| 9[c] |  **2.72** |  **2.73** | 65 | 1.2:1 | 97:3 |

Reactions performed with 0.5 mol % $Rh(acac)(CO)_2$ and 0.55 mol % of (*S,S*)-**L2.11**; [substrate]=1.0M. [a]Branch:linear ratio determined by $^1$H-NMR analysis. [b]Enantomeric ratios dertermined by SFC analysis on chiral stationary phase.[c] *(R,R)*-**L2.11** used for this entry.

Additionally, the AHF is amenable to a large scale reaction (Scheme 2.8, eq. 1). With significantly decreased catalyst loading, 7.5 g of β-siloxy aldehyde **4.39** was produced with the same levels of enantio- and regioselectivity. When subjecting internal olefin **2.74** to the optimized reaction conditions, aldehyde **2.75** was obtained in high enantioselectivity with 7.8:1 regioselectivity favoring insertion at the carbon closest to the protected oxygen. This is a rare example of a regioselective AHF of an internal olefin. Most examples of AHF of internal olefins are limited to activated olefins such as cyclic dihydrofurans, pyrrolines, and β-methyl styrenes.[27]

**Scheme 2.8: Large Scale AHF and AHF of Internal Olefins**

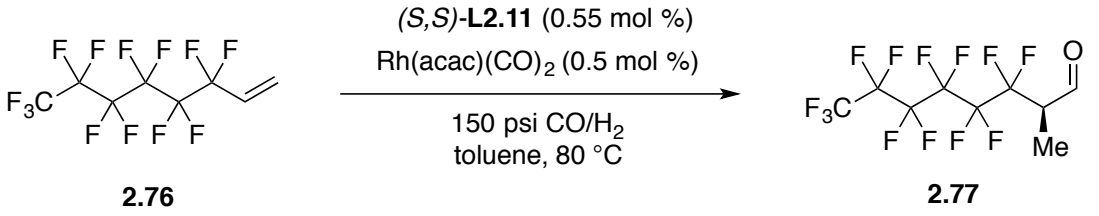



[27] (a) Xu, K; Zheng, X.; Wang, Z.; Zhang, Z. *Chem.-Eur. J.* **2014**, *20*, 4357. (b) Chikkali, S. H.; Bellini, R.; de Bruin, B.; van der Vlugt, J .I.; Reek, J. N. H. *J. Am. Chem. Soc.* **2012**, *134*, 6607. (c) Watkins, A. L.; Hashiguchi, B. G.; Landis, C. R. *Org. Lett.* **2008**, *10*, 4553.

### *2.3.4 Problematic Substrates for AHF with PhBPE*

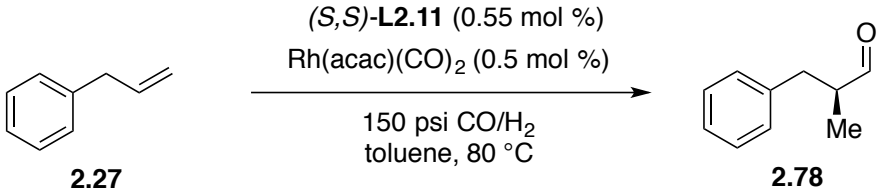
Though the scope of the AHF with PhBPE **L2.11** is fairly broad, we did run into several issues when attempting to further expand the scope. With specific substrates we observed post-hydroformylation racemization of the product aldehydes during the reaction (Scheme 2.9). AHF of polyfluoronated 1-octene **2.76** lead to very high regioselectivities, likely due to the electron-withdrawing nature of the chain, but very low enantioinduction. At shorter reaction times, the enantioselectivity was increased slightly, indicating that post-reaction racemization occurred under the reaction conditions. We predicted that due to the increased acidity of the $\alpha$-proton, racemization would be difficult to avoid. This racemization was also observed with allyl benzene **2.27** (Scheme 2.9).

**Scheme 2.9: Asymmetric Hydroformylation of Olefins Leading to Product Racemization**




**2.76** **2.77**

| entry | time | b:l | er |
|---|---|---|---|
| 1 | 1 h | > 25:1 | 54:46 |
| 2 | 30 min | > 25:1 | 60:40 |




**2.27** **2.78**

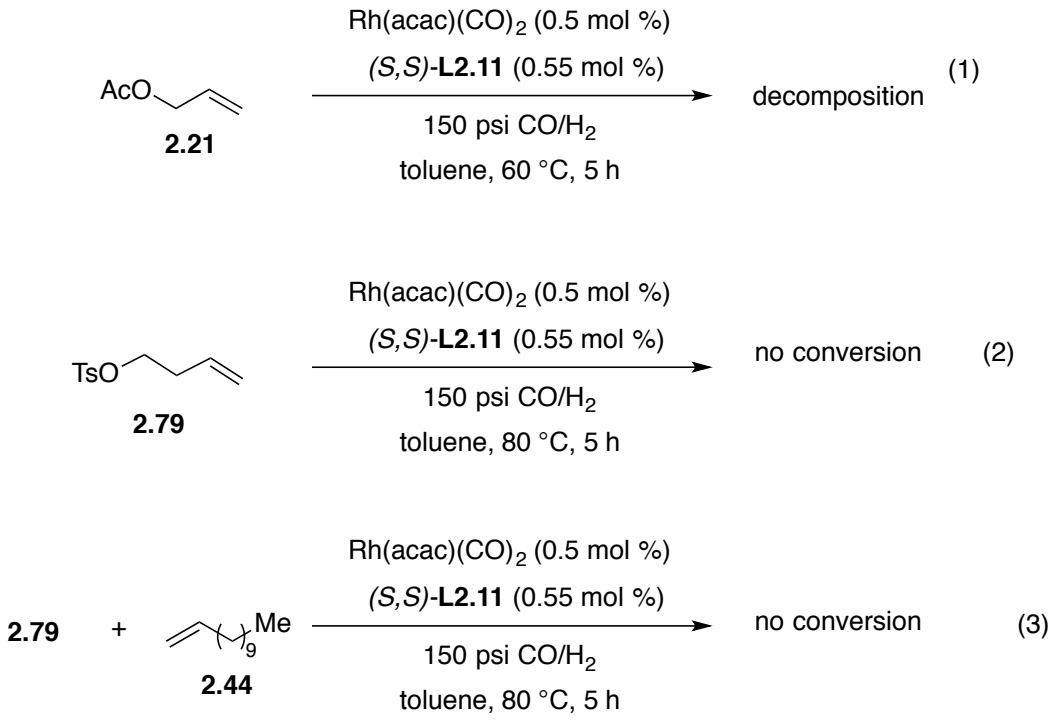
| entry | time | b:l | er |
|---|---|---|---|
| 1 | 14 h | 0.6:1 | 51:49 |
| 2 | 5 h | 0.7:1 | 60:40 |

We also discovered that allyl acetate **2.21** and other substrates with allylic leaving groups decomposed under the reaction conditions (Scheme 2.10, eq. 1). This could be due to the formation of a rhodium π-allyl intermediate by oxidative addition to the allyl electrophile.[28] Alkenes containing organosulfonates were also not tolerated in the reaction, leading to no conversion of the starting material (Scheme 2.10, eq. 2). We performed an AHF reaction where equal amounts of **2.79** and 1-dodecene **2.44** were

[28] Evans, A. P.; Tsuji, J. In *Modern Rhodium-Catalyzed Organic Reactions*; WILEY-VCH: Germany, **2005**; p 191-212, and references therein.

mixed; this reaction again did not proceed for either b or **2.79** (Scheme 2.10 eq. 3). This indicates that the sulfonate may bind to the catalyst irreversibly, shutting down catalysis.

**Scheme 2.10: Decomposition and Inhibition during Investigation of AHF Scope**




*2.3.5 Correlation of AHF Regioselectivity with Electron-Withdrawing Nature of Alkene*

We have demonstrated an efficient, highly enantioselective AHF for a variety of 1-alkenes. Throughout the scope of the AHF it is apparent that the regioselectivites differ depending on the substrate, varying from 1.2:1 to 15:1 branched to linear ratio. The results in Table 2.10 and 2.11 indicate that the stronger the electron-withdrawing nature of the substituent on the alkene, the higher the branched selectivity. We then turned

our attention to developing a predictive tool for product distribution based on this electronic influence.

In a 2013 report on oxidative Heck arylations of internal alkenes, Sigman and co-workers correlated differences in the $^{13}C$ shifts of the two alkene carbons to the regioselectivity of the reaction ($\Delta\delta\ ^{13}C$).[29] This indicates that the $\Delta\delta\ ^{13}C$, can be used as measure of alkene polarization. Using this approach, we were able to find a good correlation between $\Delta\delta^{13}C$ shifts and the regioselectivity for the reaction. Though a global correlation was not observed, by separating the substrates into two classes, oxygenation at allylic and oxygenation at the homoallylic position, we were able to find good correlations (Figure 2.1). It is possible that for all substrates inductive effects polarized the alkene and favor the branched product during AHF. However, the allylic substrates have a steeper slope showing larger jumps in branched selectivity with more polarization of the alkene. This marked jump in selectivity could be due to resonance effects ($\sigma_{C\text{-}Rh}$ to $\sigma_{C\text{-}O}$ mixing) which provide an additional stabilizing feature that operates only for the allylic ether substrates.

[29] Mei, T.-S.; Werner, E. K.; Burckel, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830.

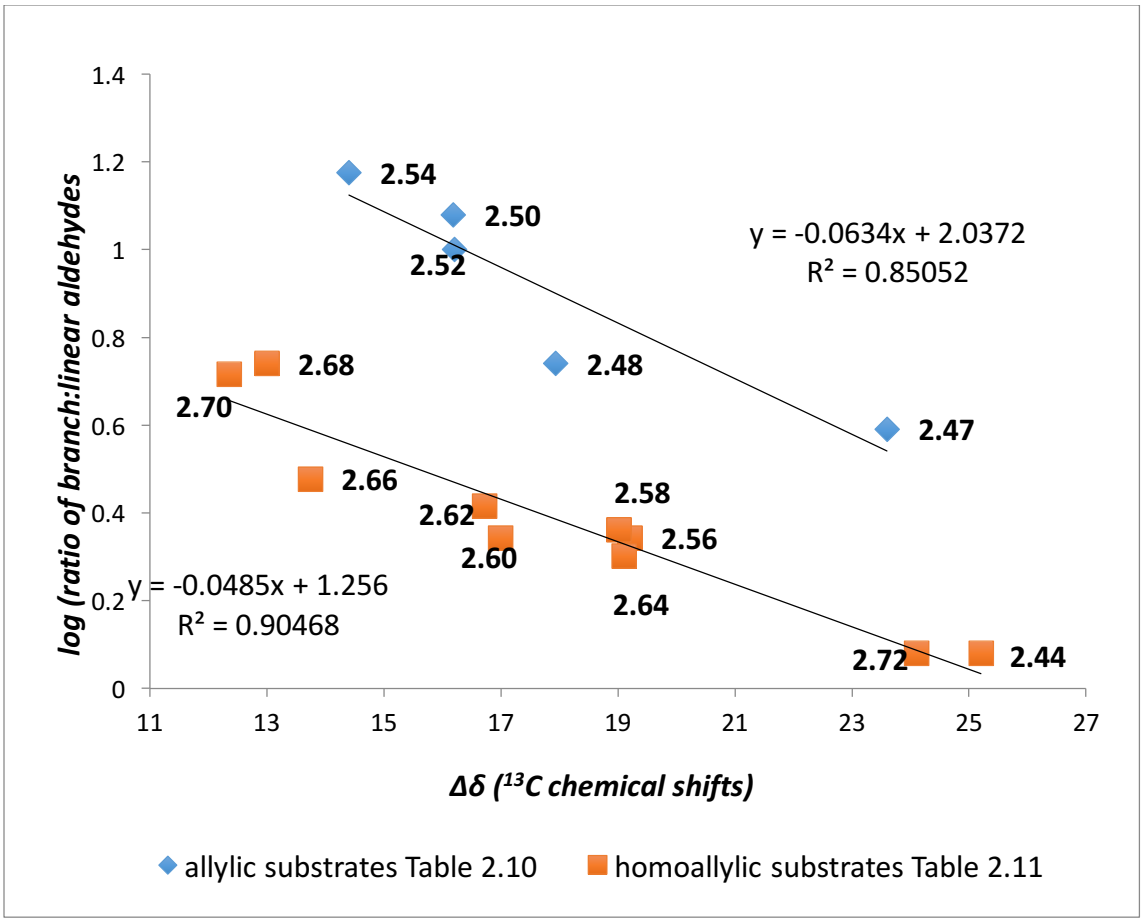



**Figure 1: Plot of $\Delta\delta$ $^{13}$C chemical shift of alkene carbons versus regioselectivity of alkene AHF.**

## 2.4 Conclusions

We have demonstrated that a rhodium catalyst with commercially available PhBPE ligand **L2.11** is efficient in the AHF of minimally and non-electronically-biased olefins. We have also shown that the method is amenable to large scale reaction with low catalyst loadings and little variation in selectivity. Remarkably, we have demonstrated that even internal olefins can give synthetically useful regio- and enantioselectivities. With our method in hand, we were then able to correlate the electron-withdrawing

nature of alkene substituents with regioselectivies of the AHF. Hopefully with this entry in AHF, we will begin to see further investigations into other ligand scaffolds and the implementation of AHF in the context of total synthesis and production of fine chemicals.

## 2.5 Experimental

### *2.5.1 General Information*

$^{1}$H-NMR spectra were recorded on a Varian Gemini-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as the following: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent), and coupling constants (Hz). Coupling constants are reported to the nearest 0.5 Hz. $^{13}$C NMR spectra were recorded on a Varian Gemini-500 (150 or 125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.23 ppm). Infrared (IR) spectra were recorded on a Burker alpha spectrophotometer, $\nu_{max}$ $cm^{-1}$. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High-resolution mass spectrometry (ESI) was performed at the Mass Spectrometry Facility, Boston College.

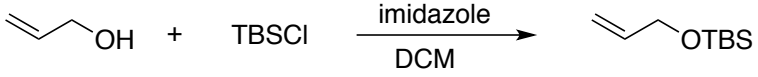
Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel ($SiO_2$, 230×450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate ($KMnO_4$) in water, 2,4-dinitrophenylhydrazine (2,4-DNP) in water/ethanol or phosphomolybdic acid (PMA)

in ethanol. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF), toluene, diethyl ether ($Et_2O$) and dichloromethane (DCM) were purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. by passing through two activated alumina columns after being purged with argon. Hydroformylation reactions were performed in an Argonaut Technologies Endeavor® Catalyst Screening System or 100-600 mL pressure vessel by Parr Instrument Company with a gage block using 1:1 $H_2$/CO supplied by Airgas, Inc. (Acetylacetonato)dicarbonylrhodium (I) [Rh(acac)$(CO)_2$] and (−)-1,2-Bis((2*R*,5*R*)-2,5-diphenylphospholano)ethane [(*S,S*)-Ph-BPE] were purchased from Strem Chemicals, Inc. and used without further purification. All other reagents were purchased from Aldrich, Alfa Aesar, or Fisher and used without further purification.

### *2.5.2 Preparation of Terminal Olefins*

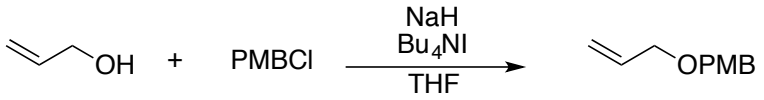
***Preparation of (Allyloxy)(tert-butyl)dimethylsilane***




*t*-Butyldimethylsilylallylether **2.47** was prepared using a known procedure and all spectral data are in accord with literature report.[30]

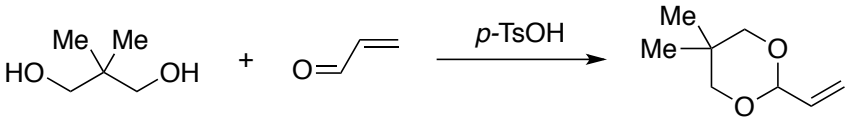
[30] Su, C. C.; Williard, P. G. *Org. Lett.* **2010**, *12*, 5378.

***Preparation of 1-((allyloxy)methyl)-4-methoxybenzene***



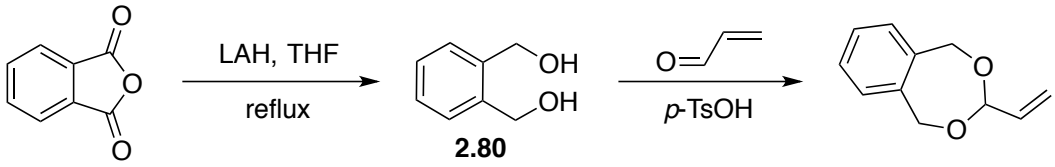

*para*-Methoxybenzyl allyl ether **2.48** was prepared using a known procedure and all spectral data are in accord with the literature report.[31]

***Preparation of 5,5-dimethyl-2-vinyl-1,3-dioxane***




Acetal **2.50** was prepared using a known procedure and all spectral data are in accord with the literature report.[32]

***Preparation of 3-vinyl-1,5-dihydrobenzo[e][1,3]dioxepine.***



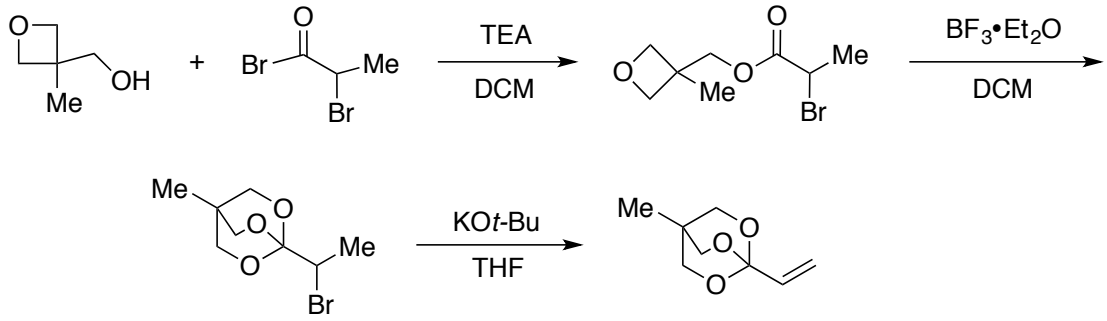

1,2-Benzenedimethanol **2.80** was prepared according to a literature procedure.[33]

Diol **2.80** (3.3 g, 23.9 mmol) and catalytic (approximately 10 mg) *p*-TsOH were dissolved in dry $CH_2Cl_2$ (12 mL) in a 50 mL round bottom flask, and stirred with $MgSO_4$ under nitrogen. Acrolein (1.59 mL, 23.9 mmol) was added dropwise to the mixture at

[31] Chênevert, R.; Dasser, M. *J. Org. Chem.* **2000**, *65*, 4529.
[32] Doumèche, B.; Archelas, A.; Furstoss, R. *Adv. Synth. Catal*. **2006**, *348*, 1948.
[33] Steffen, J.; Lei, X. G.; Li, W; Liu, Z. Q.; Turro, N. J.; Ottaviani, M. F.; Abrams, L. *J. Org. Chem.* **2002** , *67*, 2606.

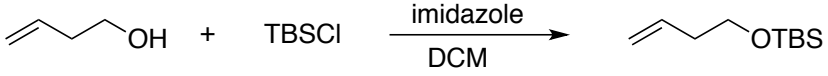
room temperature and stirred overnight. The resulting mixture was filtered and concentrated. The residue was purified by silica gel chromatography to afford the titled compound **2.52** as a colorless oil (3.3 g, 79% yield). All spectral data are in accord with literature report.[34]

***Preparation of 4-methyl-1-vinyl-2,6,7-trioxabicyclo[2.2.2]octane***




Vinyl-trioxobicyclo[2.2.2.]octane **2.54** was prepared using a known sequence from commercially available 3-methyl-3-oxetanemethanol and all spectral data are in accord with the literature.[35]

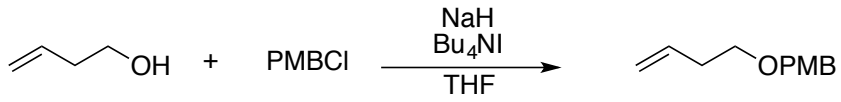
***Preparation of (but-3-en-1-yloxy)(tert-butyl)dimethylsilane***




Homoallylether **2.56** was prepared using a known a procedure and all spectral data are in accord with the literature.[36]

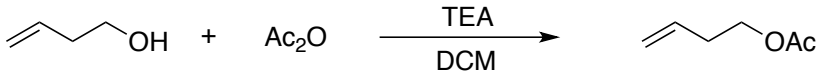
[34] Arab, K. E.; Hanan, A. Q,; Patrick, M. H. *J. Organomet. Chem.* **2002**, *656*, 168.
[35] Risi, R. M.; Burke, S. D. *Org. Lett*. **2012**, *14*, 2572.
[36] Ghosh, A. K.; Li, J. -F. *Org. Lett.* **2009**, *11*, 4164.

***Preparation of 1-((but-3-en-1-yloxy)methyl)-4-methoxybenzene***



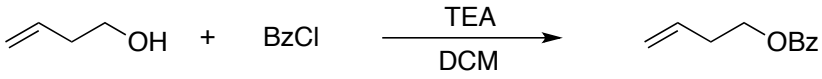

Homoallylether **2.58** (Table 2, entry 1) was prepared using known procedure and all spectral data are in accord with the literature report.[37]

***Preparation of 3-buten-1-yl acetate***




Homoallyl acetate **2.60** (Table 2, entry 1) was prepared by a known procedure and all spectral data are in accord with the literature report.[38]

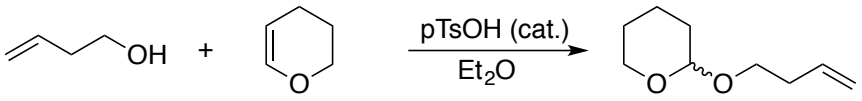
***Preparation of but-3-en-1-yl benzoate***




Homoallyl benzoate **2.62** (Table 2, entry 1) was prepared by a known procedure and all spectral data are in accord with the literature report.[39]

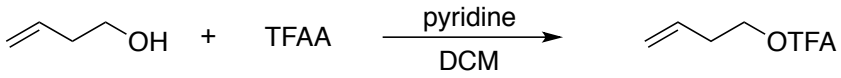
***Preparation of 2-(but-3-en-1-yloxy)tetrahydro-2H-pyran***

[37] Raghavan, S.; Krishnaiah, V. *J. Org. Chem.* **2010**, *75*, 748.
[38] Fürstner, A.; Müller, T. *Synlett.* **1997**, 1997, 1010.
[39] Zhang, M.; Vedanthanm, P.; Flynn, D. L.; Hanson, P. R. *J. Org. Chem.* **2004**, *69*, 8340.



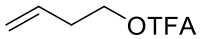

Tetrahydropyran **2.64** (Table 2, entry 1) was prepared using a known procedure and all spectral data are in accord with the literature report.[40]

***Preparation of but-3-en-1-yl 2,2,2-trifluoroacetate***

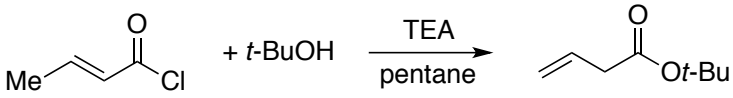



To a 25 mL round bottom flask equipped with a stir bar, was added 3-buten-1-ol (0.65 mL, 7.5 mmol) followed by dichloromethane (7.5 mL). The reaction was cooled to 0 °C in an ice bath and charged with pyridine (1.20 mL, 15.0 mmol) followed by drop-wise addition of trifluoroacetic anhydride (1.79 mL, 12.75 mmol). The reaction was allowed to stir at 0 °C for 14 hours. The reaction was then diluted with deionized water (10 mL) and extracted twice with diethyl ether (5 mL), the organic layers were combined and washed with 1M HCl (2 x 5 mL), saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic layer was then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by Kugelrohr distillation under $N_2$ at 100 °C to afford **2.66** as a light yellow oil (1.11 g, 94 % yield).

[40] Hernandez, D.; Nielsen, L.; Lindsay, K. B.; Lopez-Garcia, A.; Bjerglund, K.; Skrydstrup, T.; *Org. Lett.* **2010**, *12*, 3528.

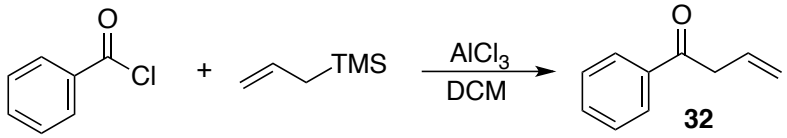
 **But-3-en-1-yl 2,2,2-trifluoroacetate (2.66)**: $^{1}$H NMR (500 MHz, $CDCl_3$): δ 5.77 (1H, ddt, *J* = 17.0 Hz, 10.0 Hz, 7.0 Hz), 5.18 (1H, q, *J* = 1.5 Hz), 5.16-5.13 (1H, m), 4.40 (2H, t, *J* = 7.0 Hz), 2.50 (2H, dq, *J* = 7.0 Hz, 1.0 Hz); $^{13}$C NMR (150 MHz, $CDCl_3$): δ 157.5 (q, *J* = 157.5), 132.3, 118.5, 114.5 (q, *J* = 283.9), 66.9, 32.5; $^{19}$F (470 Hz, CDCl3): δ −75.2; IR (neat): 2958 (m), 2925 (s), 2871 (m), 2854 (m), 1734 (s), 1458 (m), 1262 (m), 1163 (m), 1029 (w) $cm^{-1}$; HRMS-(ESI+) for $C_6H_8F_3O_2$ [M+H]: calculated: 168.0476, found 167.0471.

***Preparation of but-3-enoic acid tert-butyl ester***




*t*-Butyl ester **2.68** was prepared using a known procedure and all spectral data are in accord with the literature report.[41]

***Preparation of 1-phenyl-but-3-en-1-on***

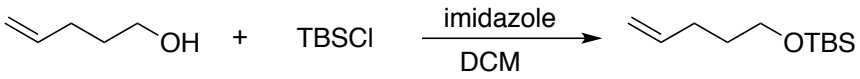



To an oven dried 50 mL round bottom flask with stir bar was added aluminum chloride (730.0 mg, 5.5 mmol). The flask was capped with a septa and purged with $N_2$. To this was added dichloromethane (20 mL) followed by dropwise addition of benzoyl chloride (0.58 mL, 5.0 mmol). The reaction was allowed to stir for 20 minutes prior to dropwise addition of allyltrimethylsilane (0.96 mL in 2.0 mL dichloromethane, 6.0 mmol).

[41] Ramachandran, P.V.; Nicponski, D.; Kim, B. *Org. Lett.* **2013**, *15*, 1398.

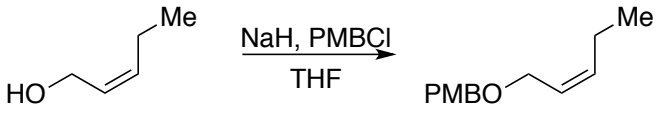
The reaction was allowed to stir for 4 hours at room temperature. The reaction mixture was quenched with ice-cold deionized water and washed three times with dichloromethane. The organic layers combined, dried over magnesium sulfate, concentrated *in vacuo* and purified on silica gel (30:1 pentane: diethyl ether) to afford **2.70** as a clear, colorless oil (866.4 mg, quantitative yield) (Table 2, entry 3). $R_f$ = 0.31 (30:1 pentane: diethyl ether, stain in $KMnO_4$). All spectral data are in accord with the literature.[42]

***Preparation of (1,1-dimethylethyl)(dimethyl)(4-pentenyloxy)silane***




Bishomoallyl ether **2.72** (Table 2, entry 4) was prepared using literature procedure and all spectral data are in accord with literature.[43]

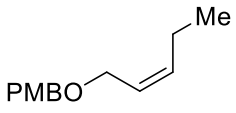
*2.5.3 Preparation of Internal Cis-Allyl Ether*




A flamed dried 100 mL round bottom flask with stir bar was charged with NaH

[42] Moriyama, K.; Takemura, M.; Togo, H. *J. Org. Chem.* **2014**, *79*, 6094.
[43] (a) Kovtonyuk, V.N.; Kobrina, L.S.; Gatilov, Y.V.; Bagryanskaya, I.Y.; Fröhlich, R.; Haufe, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1929. (b) Kwan, E.E.; Scheerer, J.R.; Evans, D.A. *J. Org. Chem.* **2013**, *78*, 175.

(360 mg, 15 mmol) and 20 mL THF under $N_2$. After cooling to 0°C, *cis*-2-penten-1-ol (1.1 mL, 11 mmol) was added dropwise *via* syringe, which was allowed to stir at 0°C for 45 min. Then $Bu_4NI$ (50 mg, catalytic) and PMBCl (1.4 mL, 10 mmol) were added sequentially at 0°C, and the solution was allowed to warm to room temperature and stir overnight. The reaction was quenched with $NH_4Cl$ aqueous solution and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organics were dried over $Na_2SO_4$, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (diethyl ether : hexanes = 1:10) to afford **2.74** as a clear, colorless oil. $R_f$ = 0.53 (6:1 hexanes: diethyl ether, stain in $KMnO_4$).




**(*Z*)-1-Methoxy-4-((pent-2-en-1-yloxy)methyl)benzene (2.74).** $^1$H NMR (500 MHz, $CDCl_3$): δ 7.27 (2H, d, *J* = 9.5 Hz), 6.88 (2H, d, *J* = 9.0 Hz), 5.60-5.54 (2H, m), 4.44 (2H, s), 4.04 (2H, d, *J* = 6.0 Hz), 3.81 (3H, s), 2.06 (2H, quin, *J* = 7.5 Hz), 0.97 (3H, t, *J* = 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 159.4, 135.6, 130.8, 129.6, 125.7, 114.0, 71.9, 65.5, 55.5, 21.1, 14.4; IR (neat): 3011 (w), 2836 (w), 1613 (m), 1513 (s), 1463 (w), 1302 (m), 1247 (s), 1172 (m), 1082 (s), 1036 (s), 820 (s) $cm^{-1}$.

### *2.5.4 Procedure of Asymmetric Hydroformylation Reactions*

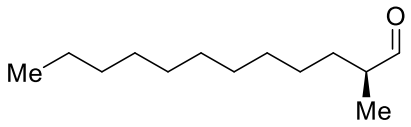
***Representative Procedure A***: (Argonaut Technologies Endeavor®, 0.5% catalyst loading): Reactions were conducted in an Argonaut Endeavor® reactor system which has eight reactor wells. Each well to be used was charged with approximately 0.5 mL of toluene in

an oven dried glass vial. The Endeavor was sealed and purged with nitrogen (4 x 100 psi). Meanwhile an oven-dried two dram-vial in dry box under an argon atmosphere was charged with alkene (1.0 mmol) and 0.5 mL of toluene followed by 0.5 mL of a rhodium/ligand stock solution (0.010 M $Rh(acac)(CO)_2$/0.011M (*S,S*)-PhBPE in toluene). The reaction mixture was then taken up in a syringe, removed from dry box and injected into the Endeavor. After injection the Endeavor was purged with nitrogen (1 x 100 psi), stirred at 250 rpm, and heated to 80 °C for 10 min. Stirring was stopped and the Endeavor charged with 150 psi of syngas (1:1 $CO/H_2$), stirring was brought to 700 rpm and heated to desired reaction temperature (80 °C). When the reaction was complete (indicated by syngas uptake) the Endeavor was vented, cooled and the vials were removed before the solvent evaporated *in vacuo.*

***Representative Procedure B:*** (Parr Reactor, 0.5% catalyst loading): To an oven-dried two dram vial with stir bar in dry box under an argon atmosphere was added alkene (1.0 mmol) and 0.5 mL of toluene. The vial was then charged with 0.5 mL of a rhodium/ligand stock solution (0.010 M $Rh(CO)_2$acac/0.011M (*S,S)*-PhBPE in toluene) and sealed with a septum cap and removed from dry box. At this time the reaction vial was brought to the pressure vessel and the septa cap pierced with a 22-gauge sterile needle and then the reactor was sealed and pressurized with 500 psi of Synthesis gas (1:1 $CO/H_2$). Once pressurized the gas was slowly allowed to vent until the parr reactor gauge read 0 psi, the parr reactor was then pressurized and vented two more times in the same manner before pressurizing to the final desired reaction pressure. Following this purging process the parr

reaction was placed in an oil bath, heated to the desired temperature and allowed to stir at 800 rpm for the desired reaction time. At the end of the reaction the oil bath was removed and parr reactor allowed to cool and then placed in an ice bath before venting. The vial was removed and the solvent evaporated *in vacuo.*

*2.5.5 Characterization of Reaction Products and Analysis of Stereochemistry*



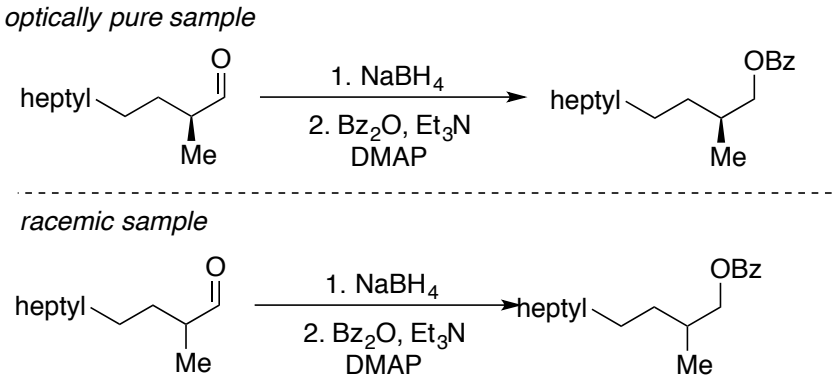

**(*S*)-2-Methyldodecanal (2.45):** The title compound was prepared *via* Representative Procedure **A** with 1-dodecene **5**. The crude reaction mixture was purified on silica gel (100% pentane to 40:1 pentane: diethyl ether) to afford a clear, colorless oil (mixture of branched and linear isomers, 196 mg, 99% yield). $R_f$ = 0.07 (40:1 pentane: diethyl ether, stain in 2,4-DNP). $[\alpha]^{22}_{D}$ = +38.667 (*c* = 0.421, $CHCl_3$, *l* = 50 mm). Spectral data are in accord with literature.[44]

***Analysis of Stereochemistry:***

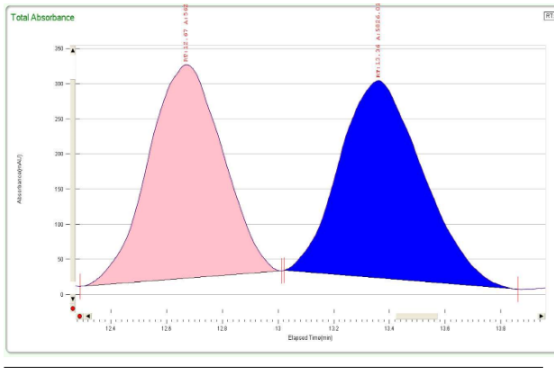
The titled compound **2.45** was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction.

[44] Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1372.

Optical purity was determined by SFC analysis of the derived benzoate. Absolute stereochemistry was determined by analogy to the optical rotation of (*S*)-2-methyldecanal reported in the literature.[45]

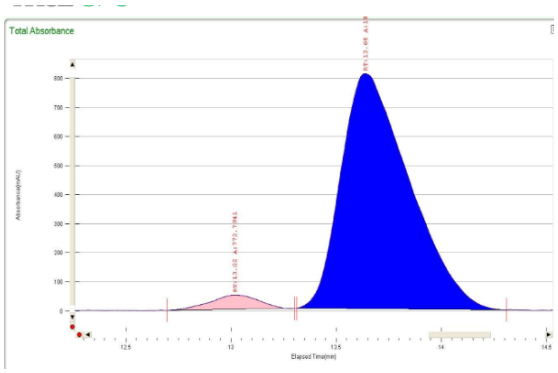



*Chiral SFC (Chiralpak, AD-H, 35 °C, 3 mL/min, 2% mixed solvent (Isopropanol:hexane = 1:1) 100 bar, 210-270 nm) – analysis of benzoate.*




*Racemic Sample*

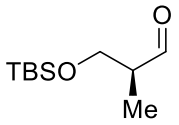
| Peak Info | | | |
|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** |
| 1 | 49.1023 | 5620.4964 | 12.67 |
| 2 | 50.8977 | 5826.0112 | 13.36 |
| Total: | 100 | 11446.5076 | |




*Enatnioenriched Sample*

| Peak Info | | | |
|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** |
| 1 | 4.057 | 773.7941 | 13.02 |
| 2 | 95.943 | 18299.1306 | 13.64 |
| Total: | 100 | 19072.9247 | |

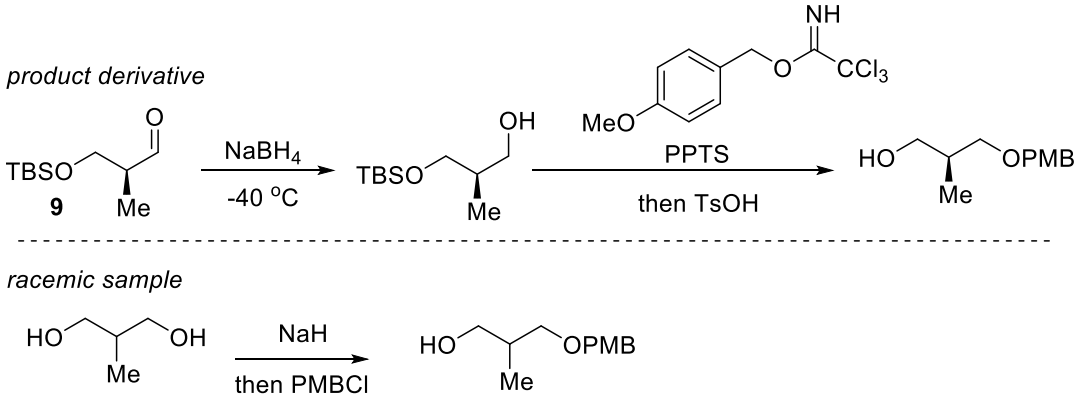
[45] Oppolzer, W.; Darcel, C.; Rochet, P.; Rosset, S.; Brabander, J. D. *Helv. Chim Acta* **1997**, *80*, 1319.




**(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropanal (2.39).** Representative procedure **A** was used with the following modifications. Olefin **2.47** (7.7 g, 45 mmol), $Rh(acac)(CO)_2$ (4.6 mg, 0.018 mmol), (*S,S*)-Ph-BPE (17.4 mg, 0.022 mmol) and toluene (5.1 mL). The reaction was stopped with full conversion observed after 8 h. The crude reaction mixture was purified on silica gel (hexane: diethyl ether = 20:1) to afford a clear colorless oil (6.54 g, 72% yield). $[\alpha]^{21}_{D}$ = +31.942 (*c* = 0.72, $CHCl_3$, *l* = 50 mm). All spectral data are in accord with literature.[46]

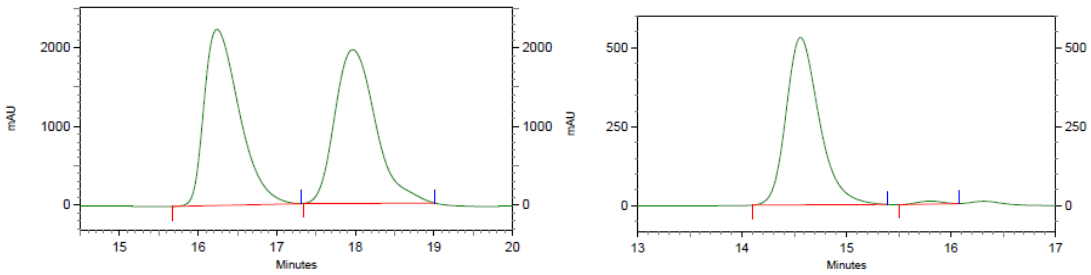
***Analysis of Stereochemistry***

The titled compound **2.39** was converted to the corresponding *p*-methoxybenzyl ether as shown below. The resulting benzyl ether was compared to racemic material prepared from 2-methyl-propan-1,3-diol. Absolute stereochemistry was assigned by comparing optical rotation to literature $[\alpha]^{22}_{D}$ = +19.5 (*c* = 1.00, $CHCl_3$, *l* = 50 mm).[46]




[46] Altendorfer, M.; Raja, A.; Sasse, F.; Irschikc, H.; Menche, D. *Org. Biomol. Chem.* **2013**, *11*, 2116.

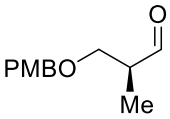
*Chiral HPLC (Chiralpak, AD-H, 25 °C, 3 mL/min, 5% Isopropanol in hexane, 220 nm) – analysis of benzyl ether.*




*Racemic Sample* *Enatnioenriched Sample*

**VWD: Signal A, 220 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 14.560 | 196559679 | 98.65 | 8892358 | 98.20 |
| 15.803 | 2689437 | 1.35 | 163313 | 1.80 |
| Totals | 199249116 | 100.00 | 9055671 | 100.00 |

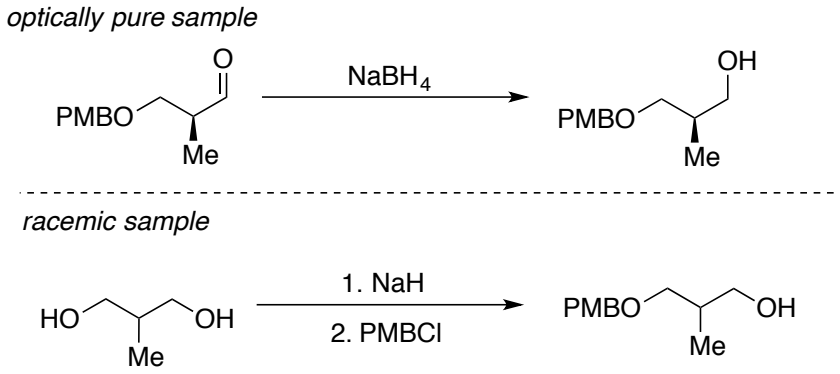



**(*S*)-3-((4-Methoxybenzyl)oxy)-2-methylpropanal (2.49).** The title compound was prepared *via* representative procedure **B** using olefin **2.48**. The crude reaction mixture was purified on silica gel (2:1 pentane: diethyl ether) to afford a clear, colorless oil (136 mg, 78% yield). $R_f$ = 0.78 (1:1 pentane: diethyl ether, stain in $KMnO_4$). $[\alpha]^{21}_D$ = +28.886 (*c* = 0.72, $CHCl_3$, *l* = 50 mm). All spectral data are in accord with literature report.[46]

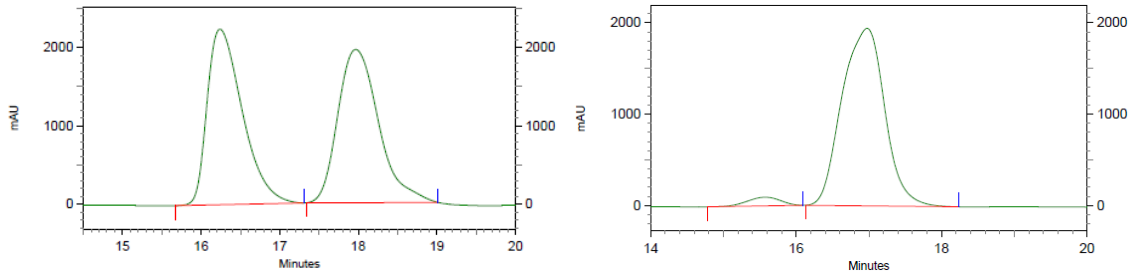
***Analysis of Stereochemistry:***

The titled compound **2.49** was reduced to the corresponding *p*-methoxybenzyl ether as shown below. The resulting benzyl ether was compared to racemic material

prepared from 2-methyl-1,3-propanediol as shown below. Absolute stereochemistry was assigned by comparing optical rotation to literature $[\alpha]^{22}_{D}$ = +30.5 (*c* = 1.00, $CHCl_3$).[46]



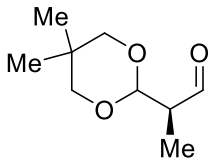

*Chiral HPLC (Chiralpak, AD-H, 25 °C, 3 mL/min, 5% Isopropanol in hexane, 220 nm) – analysis of benzyl ether.*




*Racemic Sample* *Enatnioenriched Sample*

**VWD: Signal A, 220 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 15.573 | 50852879 | 3.68 | 1602594 | 4.69 |
| 16.977 | 1332416422 | 96.32 | 32587530 | 95.31 |
| Totals | 1383269301 | 100.00 | 34190124 | 100.00 |

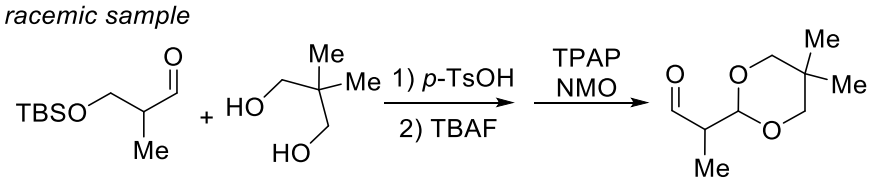



**(*R*)-2-(5,5-Dimethyl-1,3-dioxan-2-yl)propanal (2.51).** The title compound was prepared *via* representative procedure **B** using olefin **2.50**. The crude reaction mixture was purified on silica gel (4:1 pentane: diethyl ether) to afford a yellow oil (157 mg, 92% yield). $R_f$ = 0.57 (4:1 pentane:

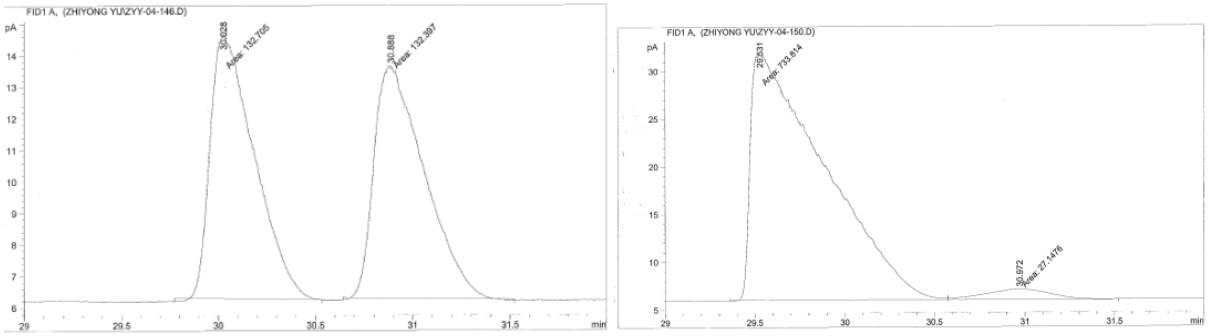
diethyl ether, stain in $KMnO_4$) $[\alpha]^{21}_D$ = +53.630 (*c* = 0.88, $CHCl_3$, *l* = 50 mm). All spectral data are in accord with literature report.[47]

***Analysis of Stereochemistry:***

The titled compound **2.51** was compared to racemic material. Absolute stereochemistry was assigned by analogy.



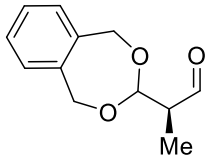

*Chiral GC (β-dex-120, supelco, 100 °C, 20 psi)-analysis of **2.51**.*



*Racemic Sample* *Enatnioenriched Sample*

| Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|---|---|---|---|---|---|---|
| 1 | 29.531 | MF | 0.4738 | 733.81372 | 25.81345 | 96.43245 |
| 2 | 30.972 | FM | 0.4149 | 27.14764 | 1.09051 | 3.56755 |

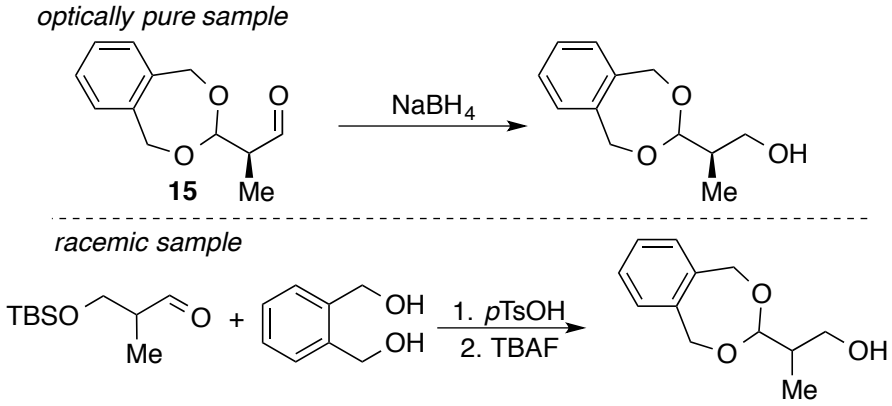
[47] Tanaka, K.; Fujimori, Y.; Saikawa, Y; Nakata, M. *J. Org. Chem.* **2008**, *73*, 6292.



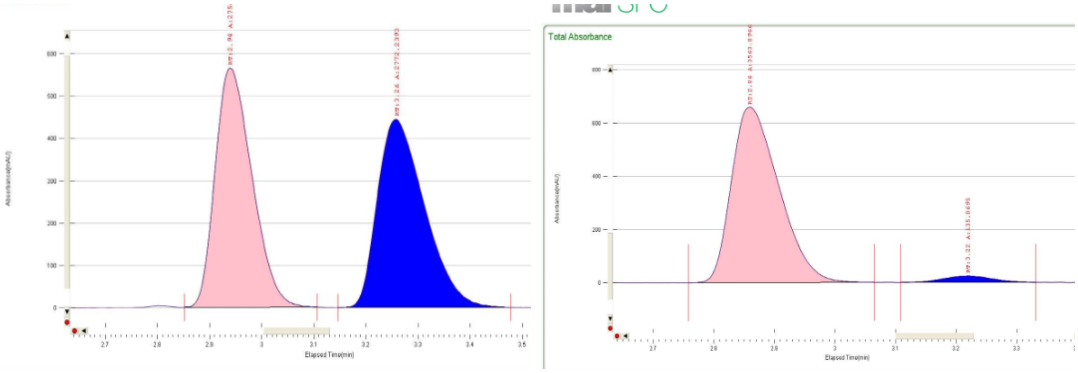
**(*R*)-2-(1,5-Dihydrobenzo[e][1,3]dioxepin-3-yl)propanal (2.53).** The title compound was prepared *via* representative procedure **B** using olefin **2.52**. The crude reaction mixture was purified on silica gel (4:1 pentane: diethyl ether) to afford a white solid (185 mg, 90% yield). $R_f$ = 0.17 (4:1 pentane: diethyl ether, stain in CAM) $^1$H NMR (500 MHz, $CDCl_3$): δ 9.80 (1H, d, *J* = 2.0 Hz), 7.28-7.21 (4H, m), 5.09 (1H, d, *J* = 6.0 Hz), 4.97 (1H, d, *J* = 14.5 Hz), 4.96 (1H, d, *J* = 14.5 Hz), 4.92 (1H, d, 1H, d, *J* = 14.0 Hz), 4.90 (1H, d, *J* = 14.5 Hz), 2.79 (1H, qd, *J* = 7.0, 2.0 Hz), 1.18 (3H, d, *J* = 7.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 202.7, 139.21, 139.20, 128.1, 127.9, 109.1, 73.5, 73.0, 51.3, 9.7; IR (neat): 2960 (w), 2848 (w), 1724 (s), 1454 (m), 1373 (m), 1101 (s), 1043 (s), 1030 (s), 773 (m), 738 (s); HRMS-(ESI+) for $C_{12}H_{18}NO_3$ $[M+NH_4]^+$: calculated: 224.1287, found: 224.1278. $[\alpha]^{21}_D$ = +46.492 (*c* = 0.90, $CHCl_3$, *l* = 50 mm).

***Analysis of Stereochemistry:***

The titled compound **2.53** was converted to the corresponding alcohol as shown below. The resulting alcohol was compared to racemic material prepared from racemic aldehyde as shown below. Absolute stereochemistry was assigned by analogy.



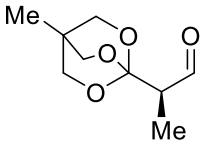
*Chiral SFC (Chiralpak, AS-H, 35 °C, 5 mL/min, 5% Isopropanol, 100 bar, 210-270 nm) – analysis of alcohol.*




*Racemic Sample* *Enatnioenriched Sample*

| Peak Info | | | |
|---|---|---|---|
| Peak No | % Area | Area | RT (min) |
| 1 | 49.8582 | 2756.5624 | 2.94 |
| 2 | 50.1418 | 2772.2393 | 3.26 |
| Total: | 100 | 5528.8017 | |

| Peak Info | | | |
|---|---|---|---|
| Peak No | % Area | Area | RT (min) |
| 1 | 96.3276 | 3563.8966 | 2.86 |
| 2 | 3.6724 | 135.8695 | 3.22 |
| Total: | 100 | 3699.7661 | |



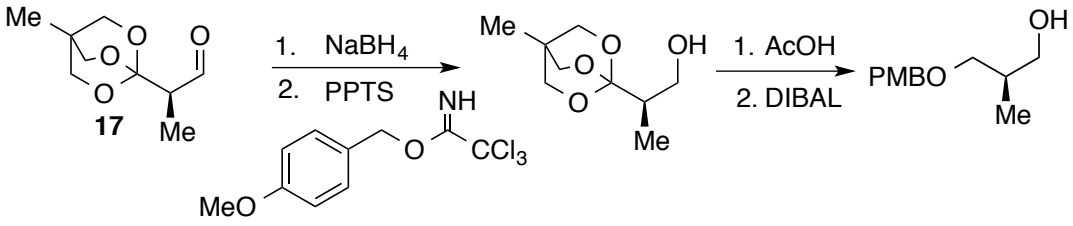

**(*R*)-2-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propanal (2.55).** The title compound was prepared *via* representative procedure **B** using olefin **2.54**. The crude reaction mixture was purified on silica gel (1:1 pentane: diethyl ether) to afford a white solid (185 mg, 90% yield). $R_f$=0.8 (1:1 pentane: diethyl ether, stain in 2,4-DNP). $[\alpha]^{21}_D$ = +65.933 (*c* = 0.72, $CHCl_3$, *l* = 50 mm). All spectral data are in accord with literature report.[48]

***Analysis of Stereochemistry:***

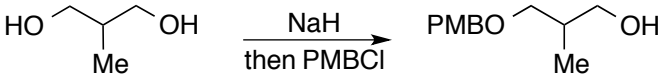
[48] Risi, R. M.; Burke, S. D. *Org. Lett*. **2012**, *14*, 2572.

The titled compound **2.55** was converted to corresponding *p*-methoxybenzyl ether as shown below. The resulting benzyl ether was compared to racemic material prepared from 2-methyl-1,3-propanediol as shown below.

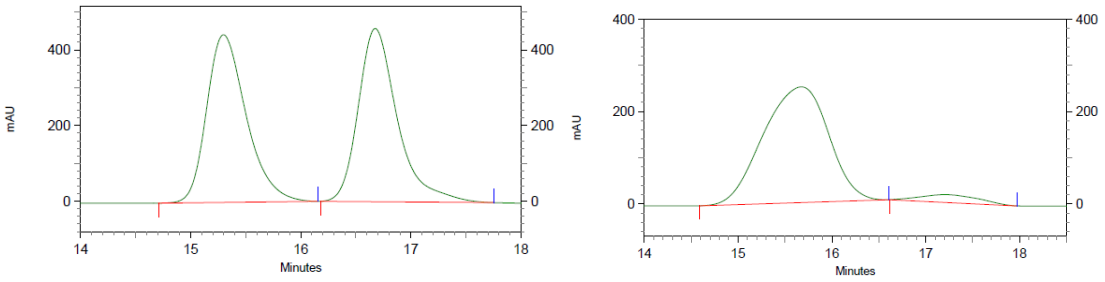
*optically pure sample*




*racemic sample*

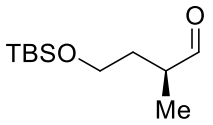



*Chiral HPLC (Chiralpak, AD-H, 25 °C, 1 mL/min, 5% Isopropanol in hexane, 220 nm) – analysis of benzyl ether.*




**VWD: Signal A,**
**220 nm Results**

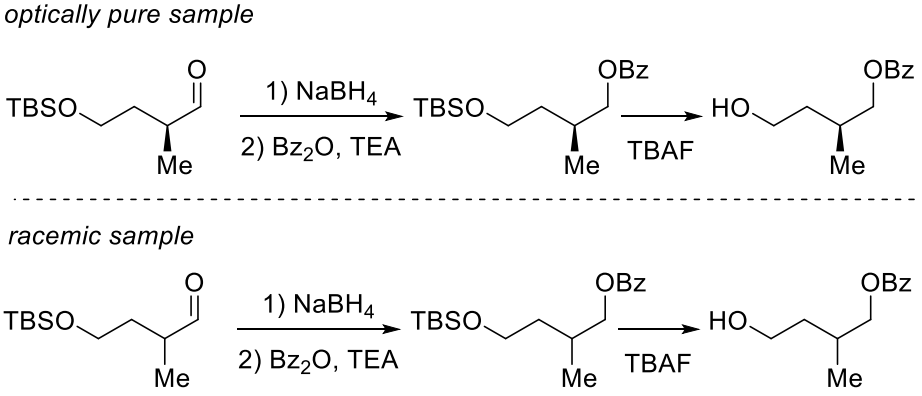
| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 15.673 | 203707854 | 94.27 | 4201524 | 93.65 |
| 17.203 | 12373743 | 5.73 | 284950 | 6.35 |
| Totals | 216081597 | 100.00 | 4486474 | 100.00 |




**(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methylbutanal (2.57).** The titled compound was prepared via representative procedure **A** with olefin **2.56**. The crude reaction mixture was purified on silica gel (20:1 hexane: diethyl ether) to afford a clear, colorless oil (138 mg, 64% yield). $[\alpha]^{22}_{D}$ = +18.347 (*c* = 1.0, $CHCl_3$. *l* = 50 mm). All spectral data are in accord with literature.[49]

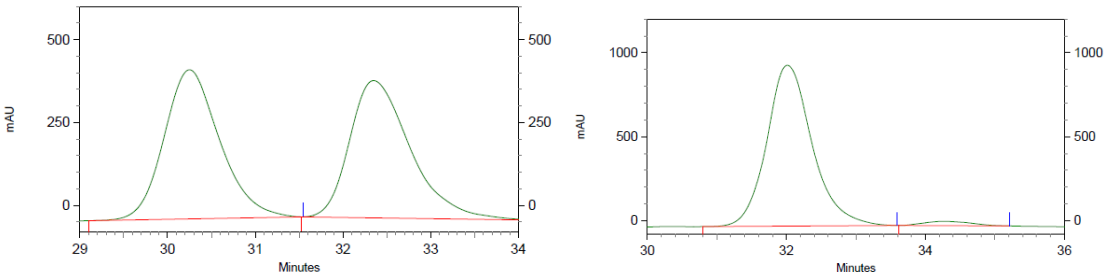
***Analysis of Stereochemistry:***

The titled compound was subjected to $NaBH_4$ reduction followed by benzoate protection and TBS removal. The analogous racemic material was prepared by employing $PPh_3$ as ligand in hydroformylation of olefin **2.56**. Optical purity was determined by chiral HPLC analysis of the derived alcohol. Absolute stereochemistry was determined by analogy the optical rotation reported in the literature.[49]



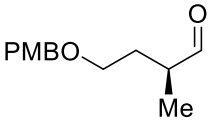

*Chiral HPLC (Chiralpak, AD-H, 25 °C, 1 mL/min, 3 % Isopropanol in hexane, 220 nm) – analysis of alcohol.*

[49] (a) Fürst, R.; Rinner, U. *J. Org. Chem*. **2013**, *78*, 8748. (b) Enders, D.; Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M. *Chem. Eur. J*. **2002**, *8*, 4272.




**VWD: Signal A, 220 nm Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 32.013 | 730462339 | 97.33 | 16051857 | 97.44 |
| 34.263 | 20002090 | 2.67 | 422068 | 2.56 |
| Totals | 750464429 | 100.00 | 16473925 | 100.00 |



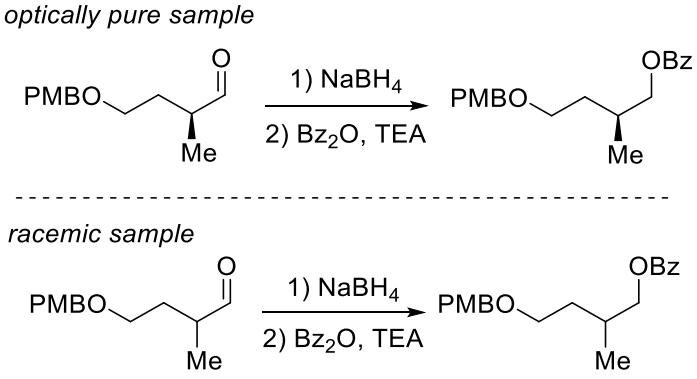

**(*S*)-4-((4-Methoxybenzyl)oxy)-2-methylbutanal (2.59**): The titled compound was prepared *via* Representative Procedure **A** with olefin **2.58**. The crude reaction mixture was purified on silica gel (10:1 pentane: diethyl ether) to afford a clear, colorless oil (133 mg, 60% yield). $R_f$ =0.17 (5:1 pentane: diethyl ether, stain $KMnO_4$). $[\alpha]^{22}_D$ = +15.453 (*c* = 0.522, $CHCl_3$, *l* = 50 mm). All spectral data are in accord with the literature.[50]

***Analysis of Stereochemistry:***

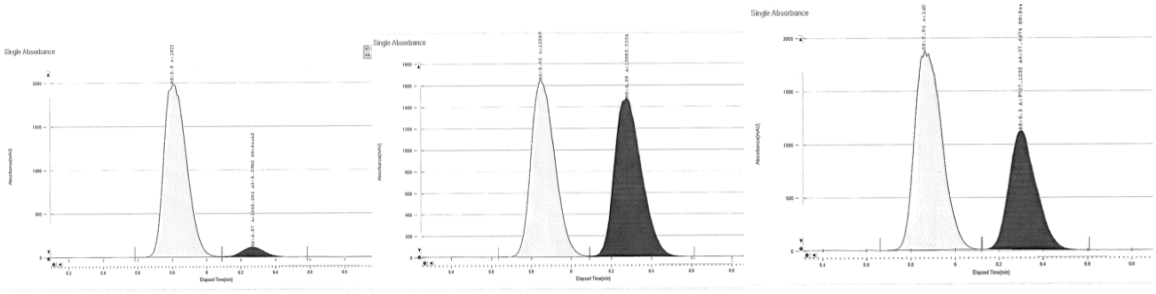
The title compound was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound as compared to

[50] Takagi, R.; Tsuyumine, S.; Nishitani, H.; Miyanaga, W.; Ohkata, K. *Aust. J. Chem.* **2004**, *57*, 439.

racemic product. Absolute stereochemistry was determined by comparing to the optical rotation reported in the literature.[51]

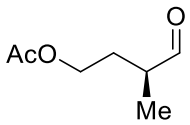



*Chiral SFC (OD-H, Chiralpak, 215nm, 3.0 mL/min, 10% i-PrOH, 100 bar, 35°C)-analysis of benzoate protected compound.*



*Enatnioenriched Sample* *Racemic Sample* *Co-injection*

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 94.6018 | 18227.1122 | 5.8 | 1988.7641 | 0.008 |
| 2 | 5.3982 | 1040.081 | 6.27 | 114.1512 | 0.0087 |
| Total: | 100 | 19267.1932 | | | |



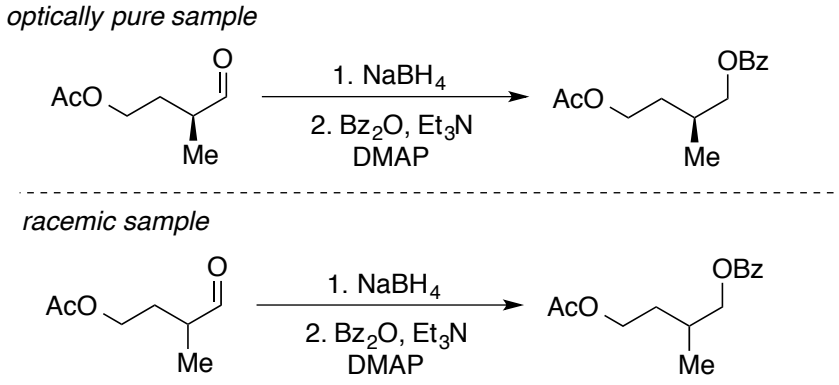

**(*S*)-4-Acetoxy-2-methyl butanal (2.61)**: The title compound was prepared with Representative Procedure **A** with olefin **2.60**. The crude reaction mixture was purified on silica gel (7:1 pentane: diethyl ether) to afford a clear,

[51] Chen, J. L.-Y.; Brimble, M. A. *J. Org. Chem.* **2011**, *76*, 9417.

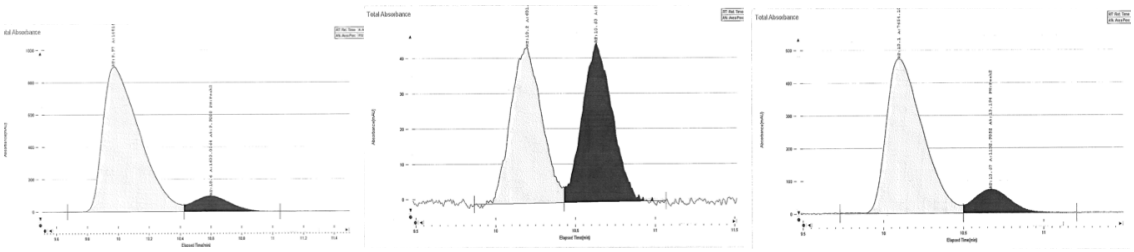
colorless oil (54 mg, 63% yield). $R_f$ = 0.26 (7:1 pentane: diethyl ether, stain in $KMnO_4$). $^1H$ NMR (500 MHz, $CDCl_3$): δ 9.63 (1H, d, *J* = 1.5 Hz), 4.14-4.11 (2H, m), 2.48 (1H, dd, *J* = 14.0 Hz, 7.0 Hz), 2.11-2.04 (1H, m), 2.02 (3H, m), 1.73-1.66 (1H, m) 1.14 (3H, dd, *J* = 7.5 Hz, 2.0 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 203.7, 170.9, 61.8, 43.5, 29.3, 20.8, 13.2; IR (neat): 2968 (w), 2932 (w), 1737 (s), 1459 (w), 1388 (w), 1367 (w), 1237 (s), 1052 (w) $cm^{-1}$; HRMS-(ESI+) for $C_7H_{12}O_3$ $[M+NH_4]^+$: calculated: 162.1130, found 162.1134. $[\alpha]^{22}_D$ = +2.245 (*c* = 0.481, $CHCl_3$, *l* = 50 mm).

***Analysis of Stereochemistry:***

The title compound was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound as compared to racemic product. Absolute stereochemistry was determined by analogy.

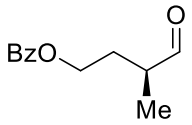



*Chiral SFC (OD-H, Chiralpak, 215nm, 3.0 mL/min, 1% i-PrOH, 100 bar, 35°C)-analysis of benzoate.*



*Enantioenriched Sample* *Racemic Sample* *Co-injection*

| Peak Info | | | | | |
|---|---|---|---|---|---|
| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
| 1 | 90.0712 | 14814.2417 | 9.97 | 898.8523 | 0.0099 |
| 2 | 9.9288 | 1633.0064 | 10.6 | 99.1684 | 0.0105 |
| Total: | 100 | 16447.2481 | | | |

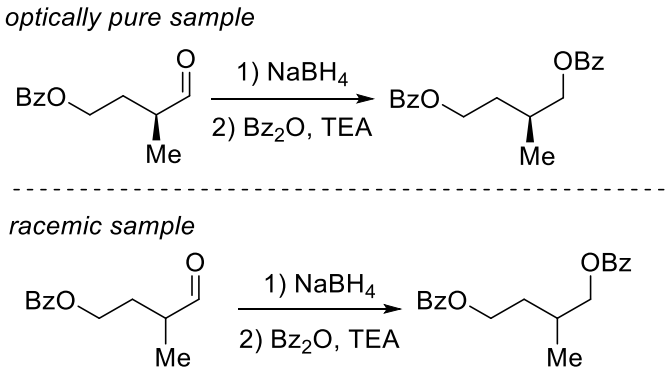



**(*S*)-3-Methyl-4-oxobutyl benzoate (2.63)**: The title compound was prepared with representative procedure **A** with olefin **2.62**. The crude reaction mixture was purified on silica gel (3:1 pentane: diethyl ether) to afford a clear, colorless oil (142 mg, 69% yield). $R_f$ = 0.19 (3:1 pentane: diethyl ether, stain in 2,4-DNP). $^1$H NMR (500 MHz, $CDCl_3$): δ 9.71 (1H, d, *J* = 1.5 Hz), 8.10-8.00 (2H, m), 7.56 (1H, tt, *J* = 7.5 Hz, 1.5 Hz), 7.44 (2H, t, *J* = 8.0 Hz), 4.44-4.37 (2H, m), 2.59 (1H, tt, *J* = 7.0 Hz, 1.5 Hz), 2.25 (1H, dq, *J* = 14.5 Hz, 6.5 Hz), 1.85 (1H, dq, *J* = 14.5 Hz, 6.5 Hz), 1.21 (3H, d, *J* = 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 203.8, 166.4, 133.0, 129.6, 128.4, 62.4, 29.5, 13.3; IR (neat): 2968 (m), 2931 (m), 1717 (s), 1452 (m), 1272 (s), 1070 (m), 936 (w), 711 (m) cm$^{-1}$; HRMS-(ESI+) for $C_{12}H_{15}O_3$ [M+H]: calculated: 207.1021, found 207.1015. $[\alpha]^{22}_D$ = +38.947 (*c* = 0.723, $CHCl_3$).

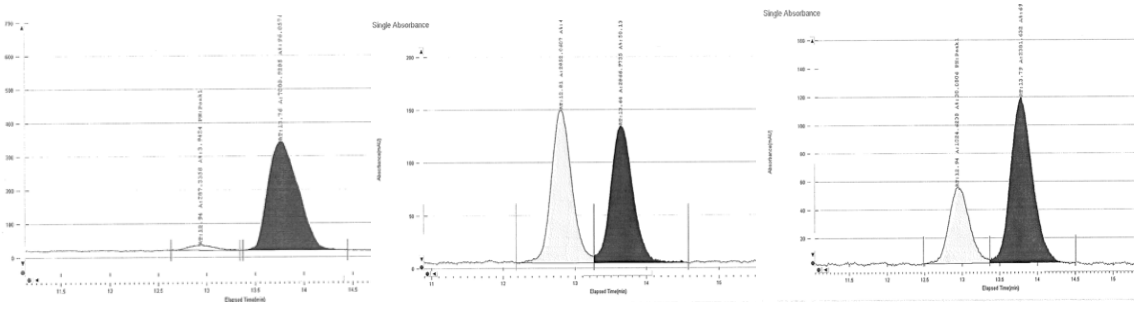
***Analysis of Stereochemistry:***

The title compound was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the

same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound as compared to racemic product. Absolute stereochemistry was determined by analogy.



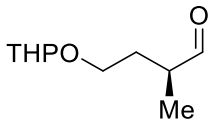

*Chiral SFC (OJ-H, Chiralpak, 215nm, 3.0 mL/min, 2% i-PrOH, 100 bar, 35°C)-analysis of bis-benzoate.*



*Enatnioenriched Sample* *Racemic Sample* *Co-injection*

Peak Info

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 3.9424 | 287.3358 | 12.94 | 15.8878 | 0.0199 |
| 2 | 96.0576 | 7000.9285 | 13.76 | 323.7626 | 0.0212 |
| Total: | 100 | 7288.2643 | | | |

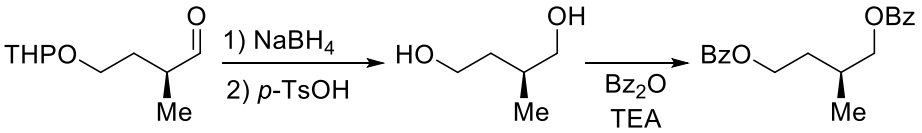



**(2*S*)-2-Methyl-4-((tetrahydro-2*H*-pyran-2-yl)oxy)butanal (2.65):** The title compound **2.65** was prepared using representative procedure **A** with olefin **2.64**. The crude reaction mixture was purified on silica gel (20:1 pentane: diethyl ether) to afford a colorless oil as a 1:1 mixture of inseparable diastereomers (114 mg, 35% yield). $R_f$ = 0.17 (10:1 pentane: diethyl ether, stain in 2,4-DNP). $^1$H NMR (500 MHz, $CDCl_3$): δ 9.65 (1H, d, *J* = 1.5 Hz), 9.64 (1H, d, *J* = 2.0 Hz), 4.56-4.55 (2H, m), 3.52-3.48 (2H, m), 3.43 (2H, m), 2.56-2.47 (2H, m), 2.03 (2H, ddt, *J* = 14.0 Hz, 7.5 Hz, 5.5 Hz), 1.80-1.66 (6H, m), 1.58-1.49 (8H, m), 1.13 (3H, d, *J* = 1.5 Hz), 1.12 (3H, d, *J* = 2.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 204.7, 98.9, 98.8, 64.8, 64.5, 62.2, 44.0, 43.8, 31.0, 30.8, 30.5, 25.4, 19.4, 13.3, 13.1; IR (neat): 2939 (m), 2872 (m), 2714 (w), 1723 (s), 1120 (m), 1022 (m), 973 (s), 732 (m), $cm^{-1}$; HRMS-(ESI+) for $C_{10}H_{19}O_3$ [M+H]: calculated: 187.1334, found 187.1344. $[\alpha]_D^{22}$ = +26.258 (*c* = 0.646, $CHCl_3$, *l* = 50 mm).

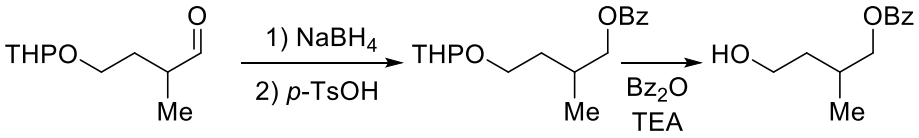
***Analysis of Stereochemistry:***

The title compound was subjected to $NaBH_4$ reduction, followed by removal of the tetrahydropyranyl ether group and bis-benzoyl protection, as depicted below. The analogous racemic material was prepared *via* the same route, using tricylcohexylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound. Absolute stereochemistry was determined by analogy.

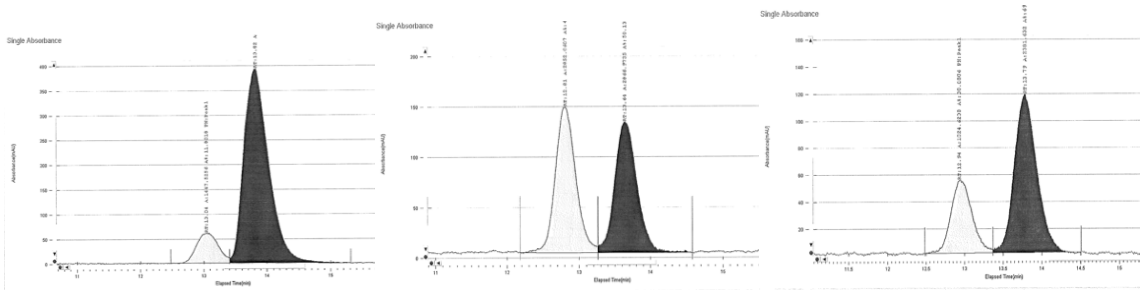
*optically pure sample*




*racemic sample*

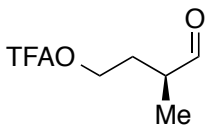



*Chiral SFC (OJ-H, Chiralpak, 215nm, 3.0 mL/min, 2% i-PrOH, 100 bar, 35°C)-analysis of benzoate protected compound.*



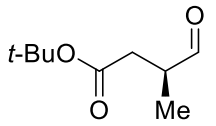
*Enantioenriched Sample* *Racemic Sample* *Co-injection*

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 11.8018 | 1447.5256 | 13.04 | 60.7848 | 0.0125 |
| 2 | 88.1982 | 10817.8139 | 13.82 | 393.3788 | 0.0133 |
| Total: | 100 | 12265.3395 | | | |




**(*S*)-3-methyl-4-oxobutyl 2,2,2-trifluoroacetate (2.67)**: The title compound was prepared using representative procedure **A** with olefin **2.66**. The crude reaction was purified on silica gel (7:1 pentane: diethyl ether) to afford a yellow oil (124 mg, 63% yield). $R_f$ = 0.25 (7:1 pentane: diethyl ether, stain in 2,4-DNP). ). $^1$H NMR (500 MHz, $CDCl_3$): δ 9.67 (1H, s), 4.43 (2H, t, *J* = 6.0 Hz), 2.50 (1H, dd, *J* = 15.0

Hz, 7.5 Hz), 2.20 (1H, dd, *J* = 13.5 Hz, 6.5 Hz), 1.79 (1H, dd, *J* = 12.5 Hz, 6.0 Hz), 1.21 (3H, d, *J* = 7.5 Hz). $^{19}$F (470 Hz, CDCl3): δ −75.0; IR (neat): 2975 (w), 1768 (m), 1711 (m), 1219 (m), 1158 (s), 816 (w). $[\alpha]^{22}_{D}$ = +16.553 (*c* = 0.252, $CHCl_3$, *l* = 50 mm).

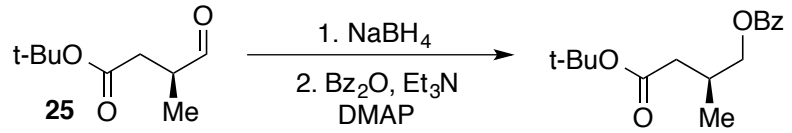



***tert*-Butyl-(*S*)-3-methyl-4-oxobutyl (2.69)**: The title compound was prepared using representative procedure **A** with olefin **2.68**. The crude reaction mixture was purified on silica gel (10:1 pentane: diethyl ether) to afford a clear, colorless oil (93 mg, 54% yield). $R_f$ = 0.12 (10:1 pentane: diethyl ether, stain in $KMnO_4$). $^1$H NMR (500 MHz, $CDCl_3$): δ 9.69 (1H, d, *J* = 1.0 Hz), 2.78 (1H, dq, *J* = 14.0 Hz, 7.0 Hz), 2.64 (1H, dd, *J* = 16.0 Hz, 7.0 Hz), 2.34 (1H, dd, *J* = 16.5 Hz, 6.5 Hz), 1.44 (9H, s); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 202.9, 170.9, 81.0, 42.8, 36.4, 28.0, 13.2; IR (neat): 2978 (w), 2933 (w), 2717 (w), 1727 (s), 1367 (w), 1156 (w) $cm^{-1}$; HRMS-(ESI+) for $C_9H_{16}O_3$ [M+H]: calculated: 173.1178, found 173.1184. $[\alpha]^{22}_{D}$ = −98.065 (*c* = 0.153, $CHCl_3$, *l* = 50 mm).

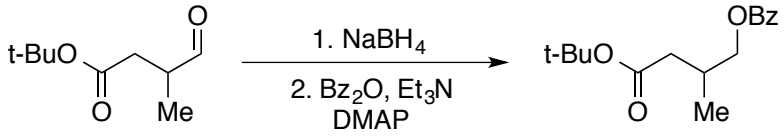
***Analysis of Stereochemistry:***

The title compound **2.69** was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound as compared to racemic product. Absolute stereochemistry was determined by analogy.

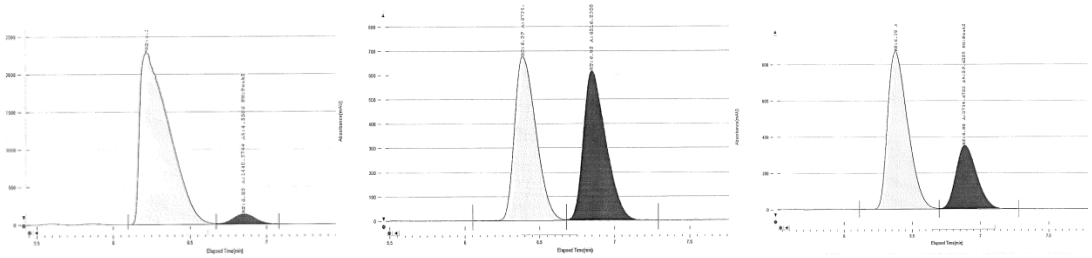
*optically pure sample*




*racemic sample*



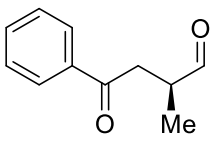

*Chiral SFC (OD-H, Chiralpak, 215nm, 3.0 mL/min, 1% i-PrOH, 100 bar, 35°C)-analysis of benzoate protected compound.*



*Enantioenriched Sample* *Racemic Sample* *Co-injection*

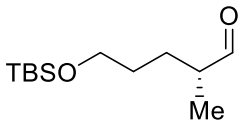
Peak Info

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 95.4414 | 30160.4156 | 6.22 | 2319.5375 | 0.0057 |
| 2 | 4.5586 | 1440.5744 | 6.85 | 138.464 | 0.0062 |
| Total: | 100 | 31600.99 | | | |




**(*S*)-2-Methyl-4-oxo-4-phenylbutanal (2.71).** The title compound was prepared using representative procedure **A** with olefin **2.70**. The crude reaction mixture was purified on silica gel (6:1 pentane: diethyl ether) to afford a clear,

colorless oil (116 mg, 66% yield). $R_f$ = 0.17 (5:1 pentane: diethyl ether, stain in $KMnO_4$). All spectral data are in accord with the literature.[52]



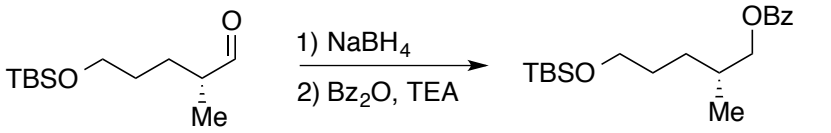

**(*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-methylpentanal (2.73)**: The titled compound **2.73** was prepared with representative procedure **A** (using (*R,R*)-Ph-BPE ligand) with olefin **2.72**. The crude reaction mixture was purified on silica gel (10:1 pentane: diethyl ether) to afford a clear, colorless oil (97 mg, 42 % yield). $R_f$ = 0.26 (10:1 pentane: diethyl ether, stain in $KMnO_4$). $[\alpha]^{22}_D$ = −46.830 (*c* = 0.556, *l* = 50 mm, $CHCl_3$). All spectral data were in accord with the literature.[53]

***Analysis of Stereochemistry:***

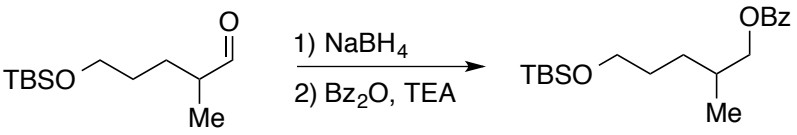
The titled compound **2.73** was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound as compared to racemic product. Absolute stereochemistry was determined by comparison with literature.[53]

[52] Zhang, J.; Xing, C.; Tiwari, B.; Chi, Y. *J. Am. Chem. Soc*. **2013**, *135*, 8113.
[53] Rentsch, A.; Kalesse, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 11381.

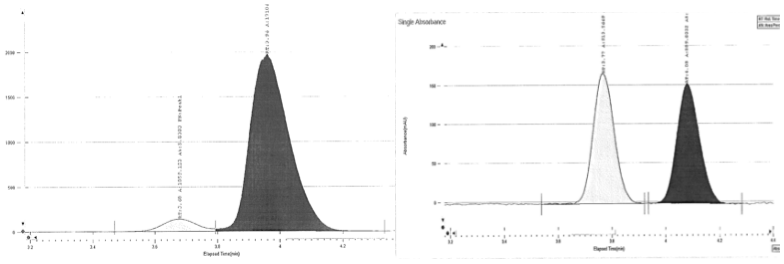
*optically pure sample*




*racemic sample*



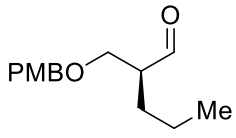

*Chiral SFC (OD-H, Chiralpak, 215nm, 3.0 mL/min, 3% i-PrOH, 100 bar, 35°C)-analysis of benzoate.*



*Enantioenriched Sample* *Racemic Sample*

Peak Info

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 5.8303 | 1059.123 | 3.68 | 138.5669 | 0.0067 |
| 2 | 94.1697 | 17106.7375 | 3.96 | 1972.3598 | 0.0072 |
| Total: | 100 | 18165.8605 | | | |

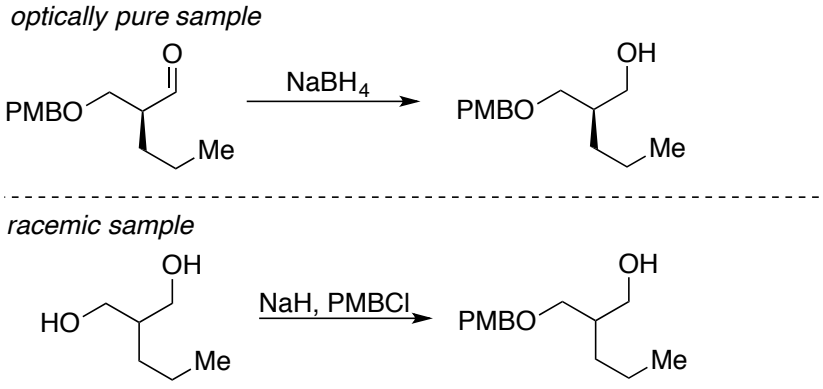



**(*S*)-2-(((4-Methoxybenzyl)oxy)methyl)pentanal (2.75).** The title compound was prepared using representative procedure **A** with olefin **2.74**. The crude reaction mixture was purified on silica gel (12:1 hexane: diethyl ether) to afford a clear, colorless oil (132 mg, 56% yield). $R_f$ = 0.35 (6:1 hexane:diethyl ether, stain in $KMnO_4$). $^1$H NMR (500 MHz, $CDCl_3$): δ 9.68 (1H, d, *J* = 2.5 Hz), 7.23 (2H, d, *J* = 9.0 Hz), 6.88 (2H, d, *J* = 8.5 Hz), 4.43 (2H, m), 3.80 (3H, s), 3.66 (1H, dd, *J* = 9.0 Hz, 7.0

Hz), 3.61 (1H, dd, *J* = 9.5 Hz, 5.0 Hz), 2.55 (1H, m), 1.65 (1H, dt, *J* = 14.5 Hz, 7.5 Hz), 1.45 (1H, dt, *J* = 14.5 Hz, 7.0 Hz), 1.33 (2H, 2H, qt, *J* = 7.0 Hz, 7.0 Hz), 0.91 (3H, t, *J* = 7.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 204.4, 159.5, 130.2, 129.4, 114.0, 73.1, 68.5, 55.5, 52.2, 28.2, 20.4, 14.3; IR (neat): 2958 (w), 2933 (w), 2864 (w), 1725 (s), 1612 (m), 1513 (s), 1465 (w), 1247 (s), 1086 (s), 1034 (s), 819 (s) $cm^{-1}$; HRMS-(ESI+) for $C_{14}H_{19}O_3$ [M+H]: calculated: 235.1334, found: 235.1343. $[\alpha]_D^{22}$ = −17.033 (c = 0.95, $CHCl_3$).

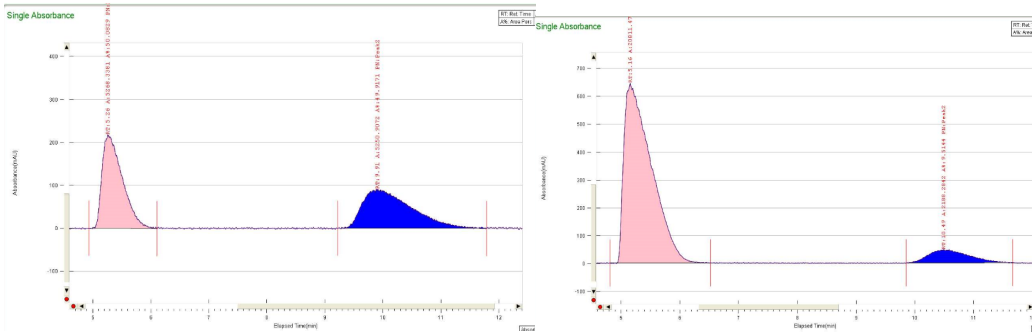
***Analysis of Stereochemistry:***

The titled compound **2.75** was converted to the corresponding alcohol as shown below. The resulting alcohol was compared to racemic material prepared from 2-propyl-propan-1,3-diol. Absolute stereochemistry was assigned by comparing optical rotation of the alcohol to literature [lit. $[\alpha]_D^{22}$ = −14.0 (*c* = 1.1, $CHCl_3$)].[54]




[54] Yadav, J. S.; Nanda, S. *Tetrahedron: Asymmetry*, **2001**, *12*, 3223.

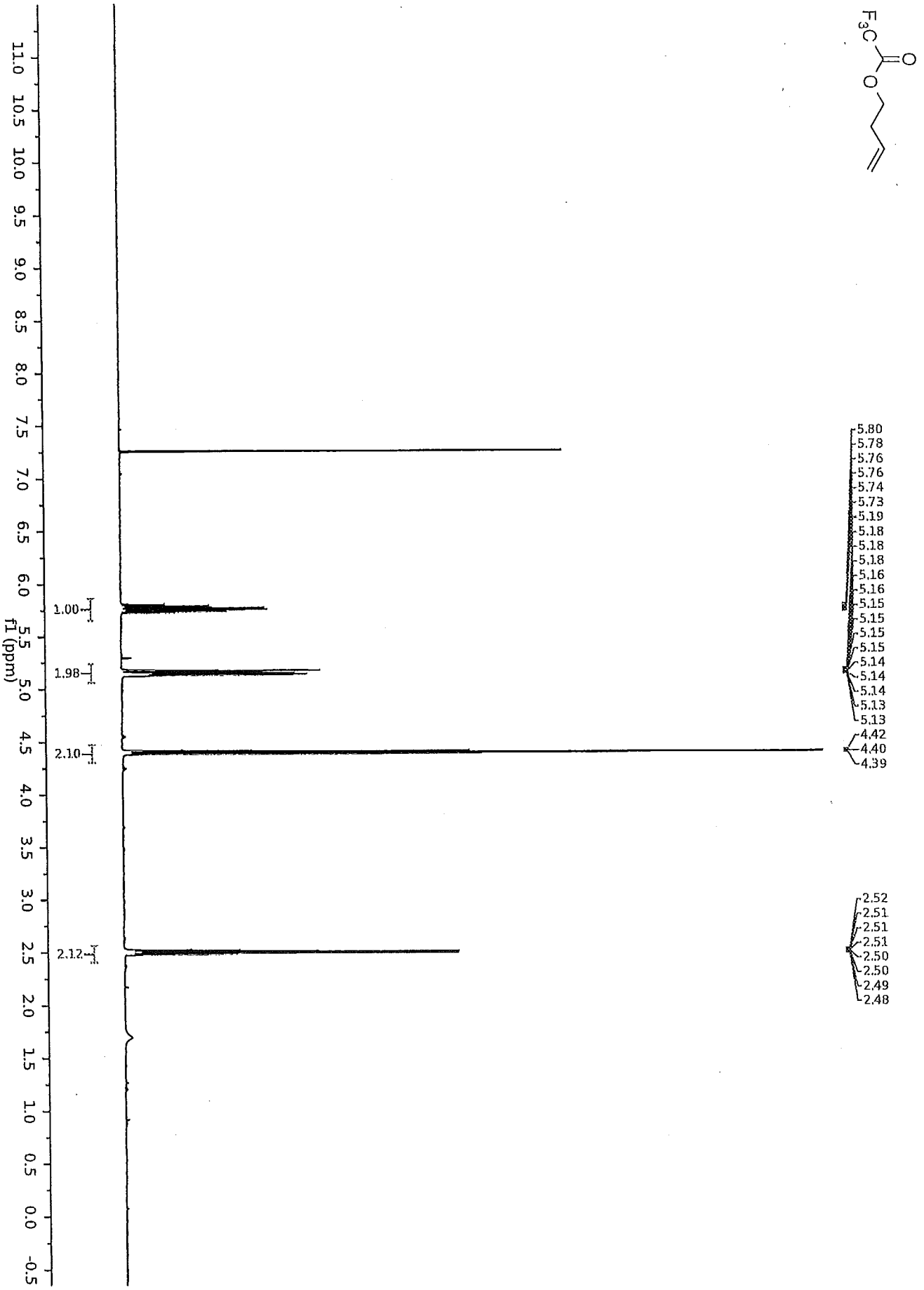
*Chiral SFC (AS-H, Chiralpak, 215nm, 3.0 mL/min, 15% i-PrOH, 100 bar, 35°C)-analysis of alcohol.*




**Peak Info**

| Peak Name | Number | Concentration | Area % | Area |
|---|---|---|---|---|
| Peak1 | 1 | 0 | 90.4856 | 20811.4749 |
| Peak2 | 2 | 0 | 9.5144 | 2188.2842 |

| Area Sum | RT (min) | St. (min) | End (min) | Height | Width (min) |
|---|---|---|---|---|---|
| | 5.16 | 4.8145 | 6.5227 | 644.6855 | 1.7099 |
| 22999.7591 | 10.49 | 9.8513 | 11.6601 | 46.2777 | 1.8104 |


F3C
O
O
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
1.00
1.98
2.10
2.12
5.80
5.78
5.76
5.76
5.74
5.73
5.19
5.18
5.18
5.18
5.16
5.16
5.15
5.15
5.15
5.15
5.14
5.14
5.14
5.13
5.13
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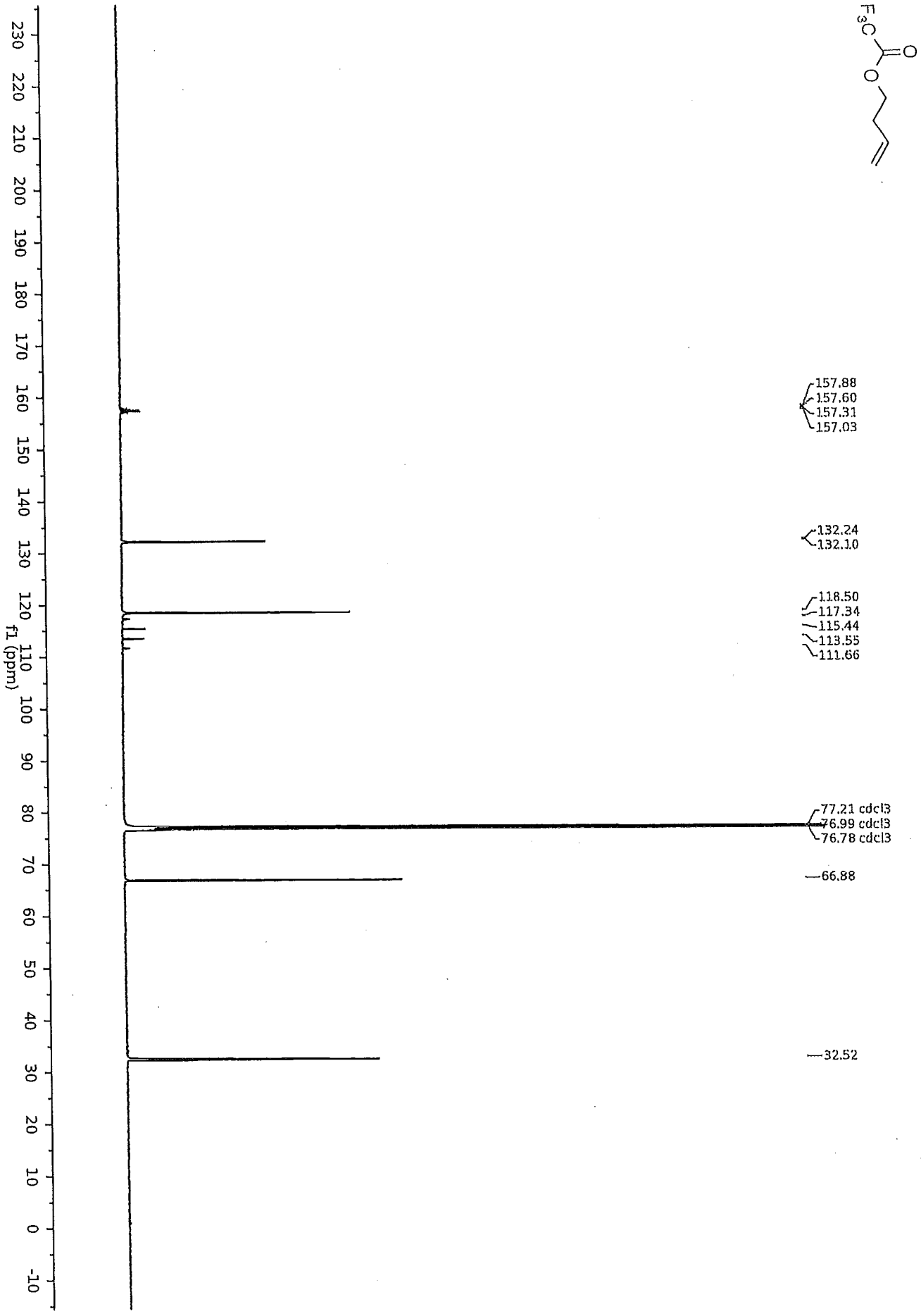
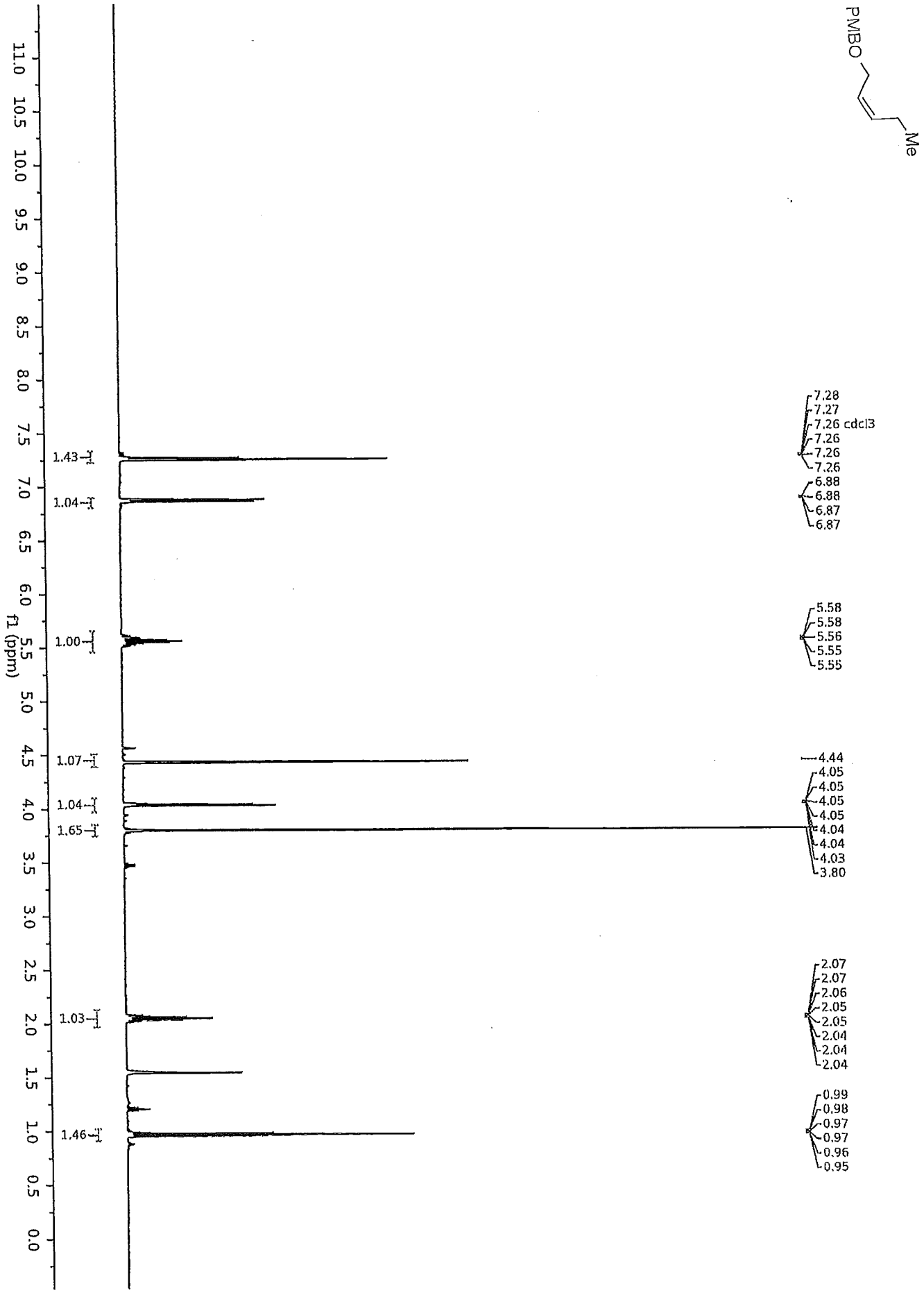
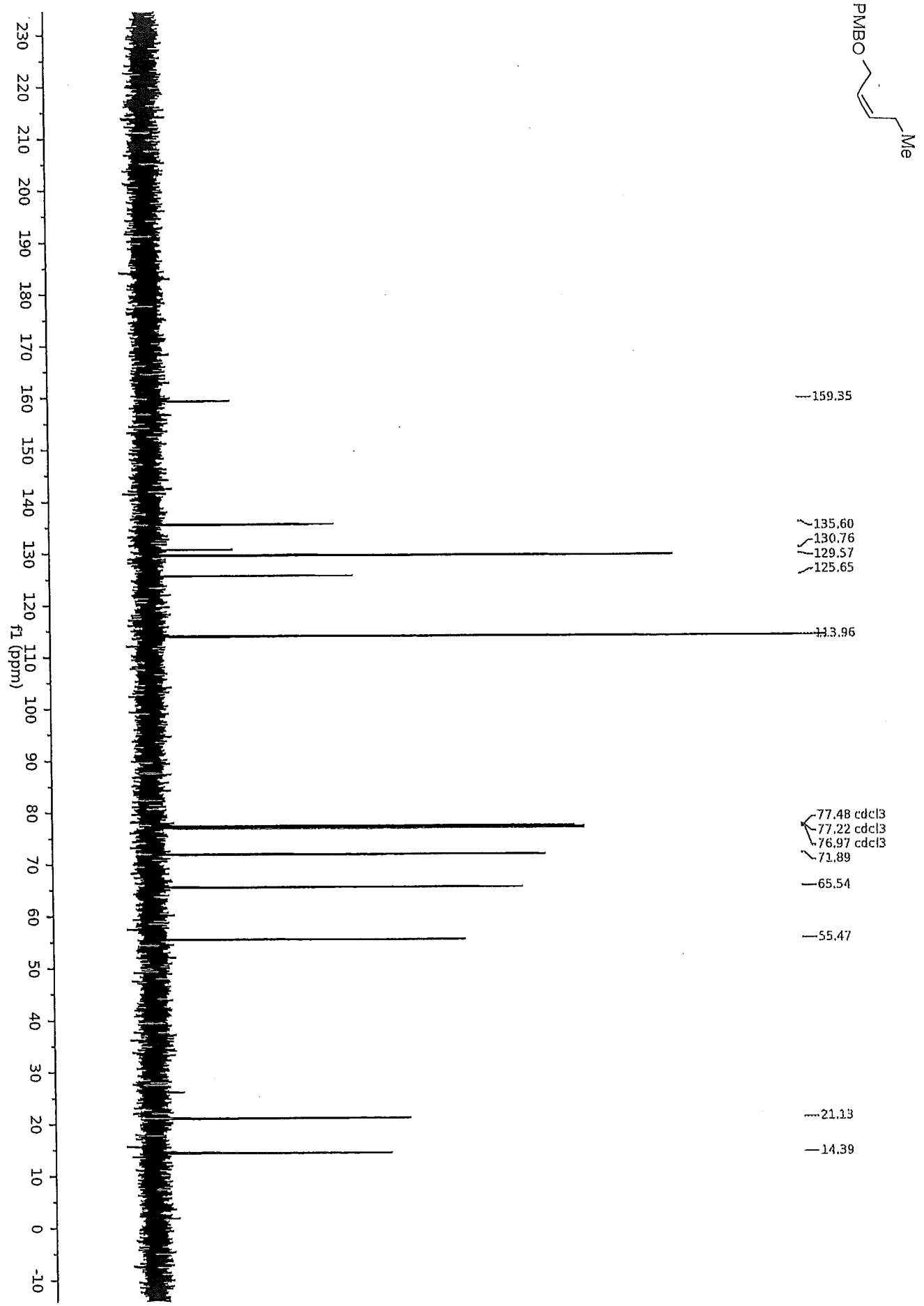
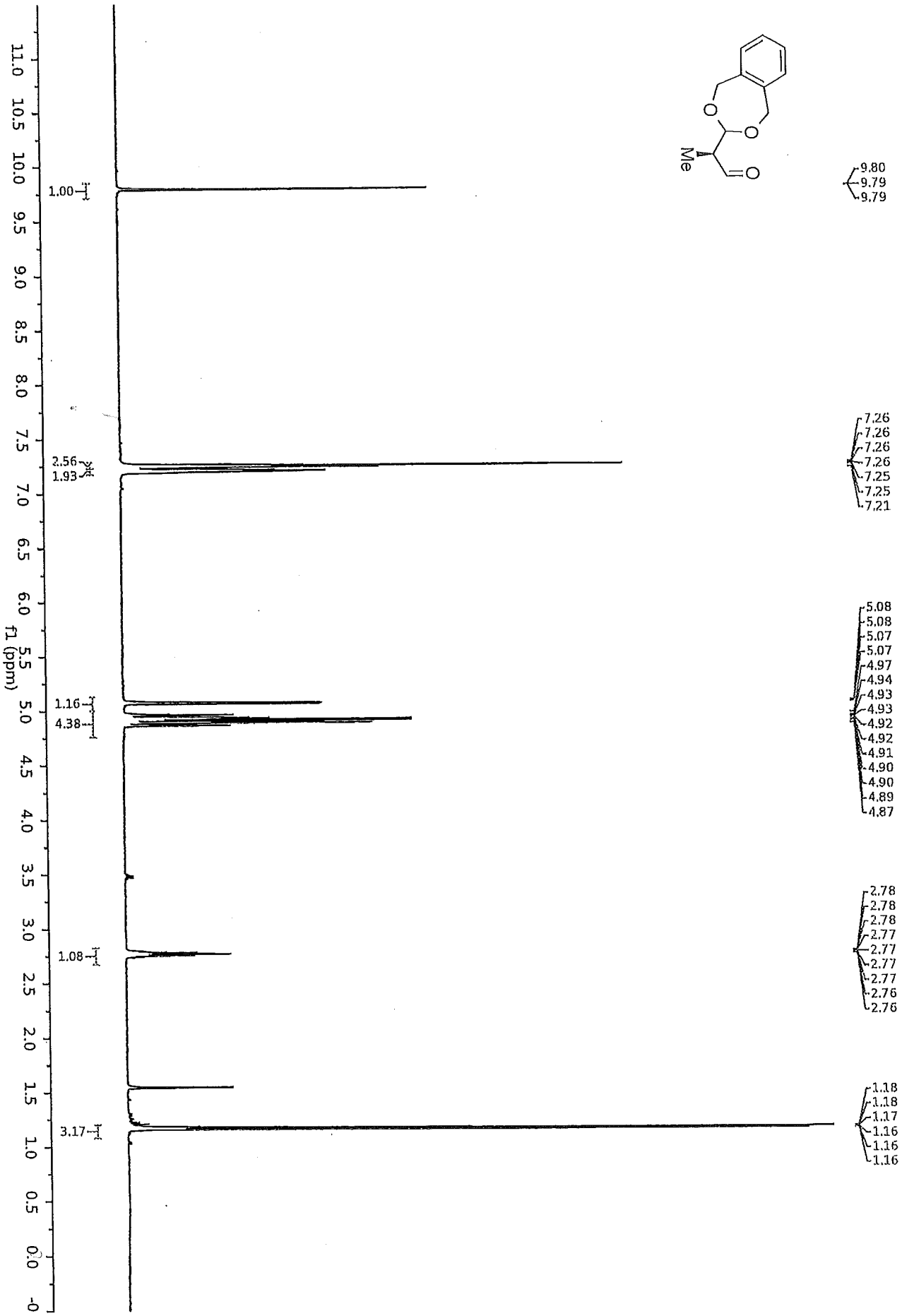
4.39
2.52
2.51
2.51
2.51
2.50
2.50
2.49
2.48


F3C
O
O
157.88
157.60
157.31
157.03
132.24
132.10
118.50
117.34
115.44
113.55
111.66
77.21 cdcl3
76.99 cdcl3
76.78 cdcl3
66.88
32.52
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


PMBO
Me
f1 (ppm)
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1.43
1.04
1.00
1.07
1.04
1.65
1.03
1.46
7.28
7.27
7.26 cdcl3
7.26
7.26
7.26
6.88
6.88
6.87
6.87
5.58
5.58
5.56
5.55
5.55
4.44
4.05
4.05
4.05
4.05
4.04
4.04
4.03
3.80
2.07
2.07
2.06
2.05
2.05
2.04
2.04
2.04
0.99
0.98
0.97
0.97
0.96
0.95


PMBO
Me
159.35
135.60
130.76
129.57
125.65
113.96
77.48 cdcl3
77.22 cdcl3
76.97 cdcl3
71.89
65.54
55.47
21.13
14.39
f1 (ppm)


f1 (ppm)
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
1.00
2.56
1.93
1.16
4.38
1.08
3.17
Me
O
O
O
9.80
9.79
9.79
7.26
7.26
7.26
7.26
7.25
7.25
7.21
5.08
5.08
5.07
5.07
4.97
4.94
4.93
4.93
4.92
4.92
4.91
4.90
4.90
4.89
4.87
2.78
2.78
2.78
2.77
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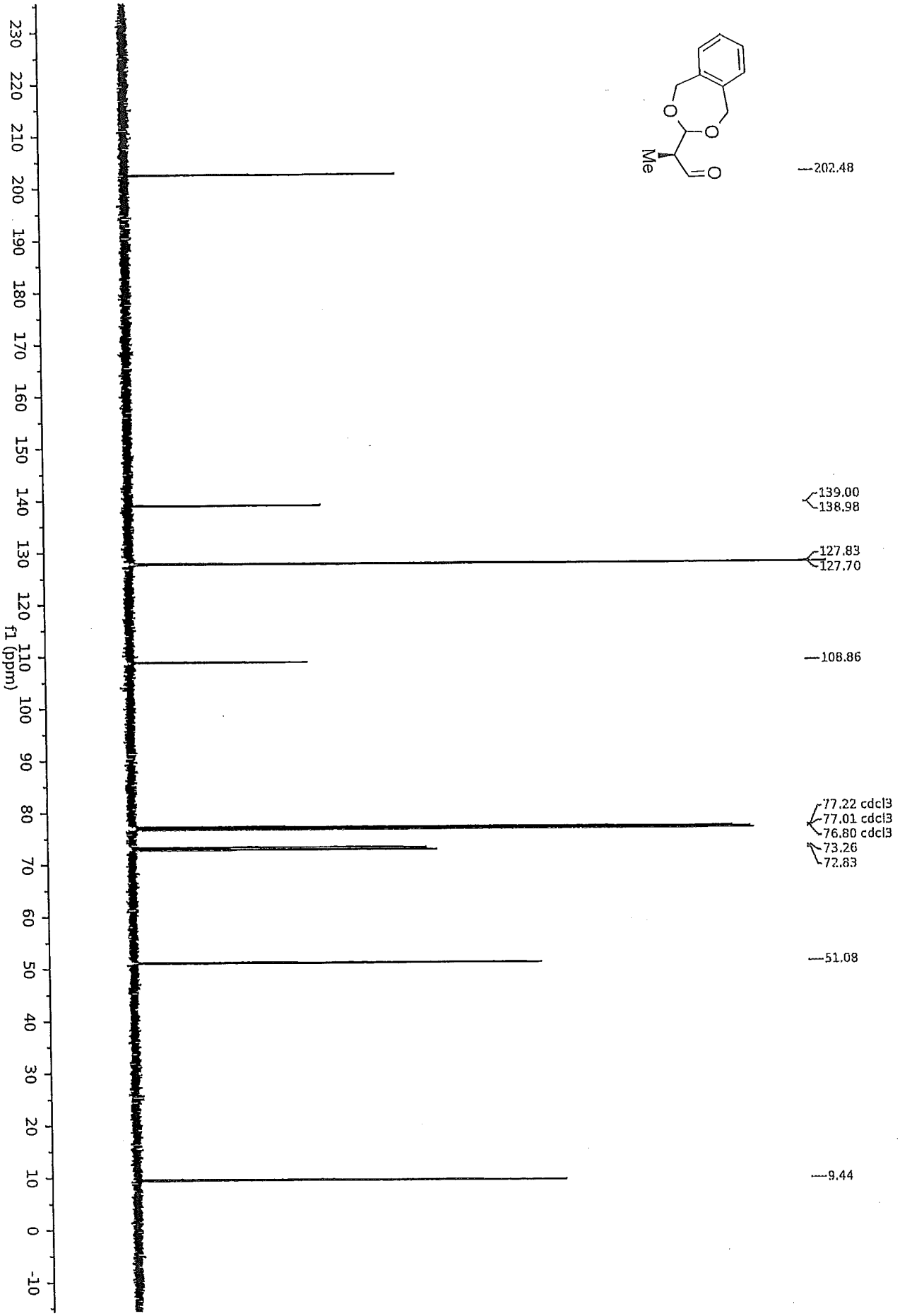
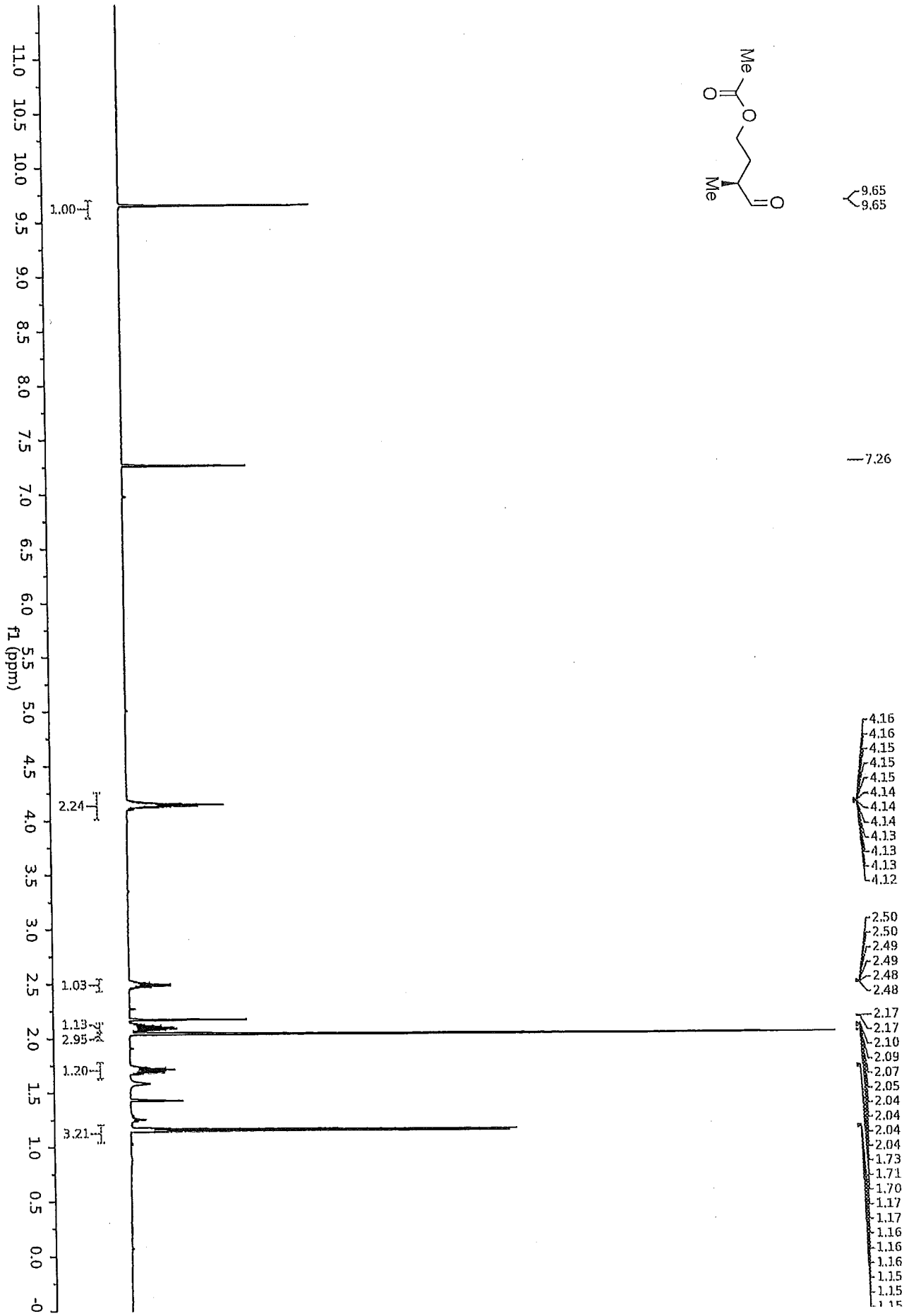
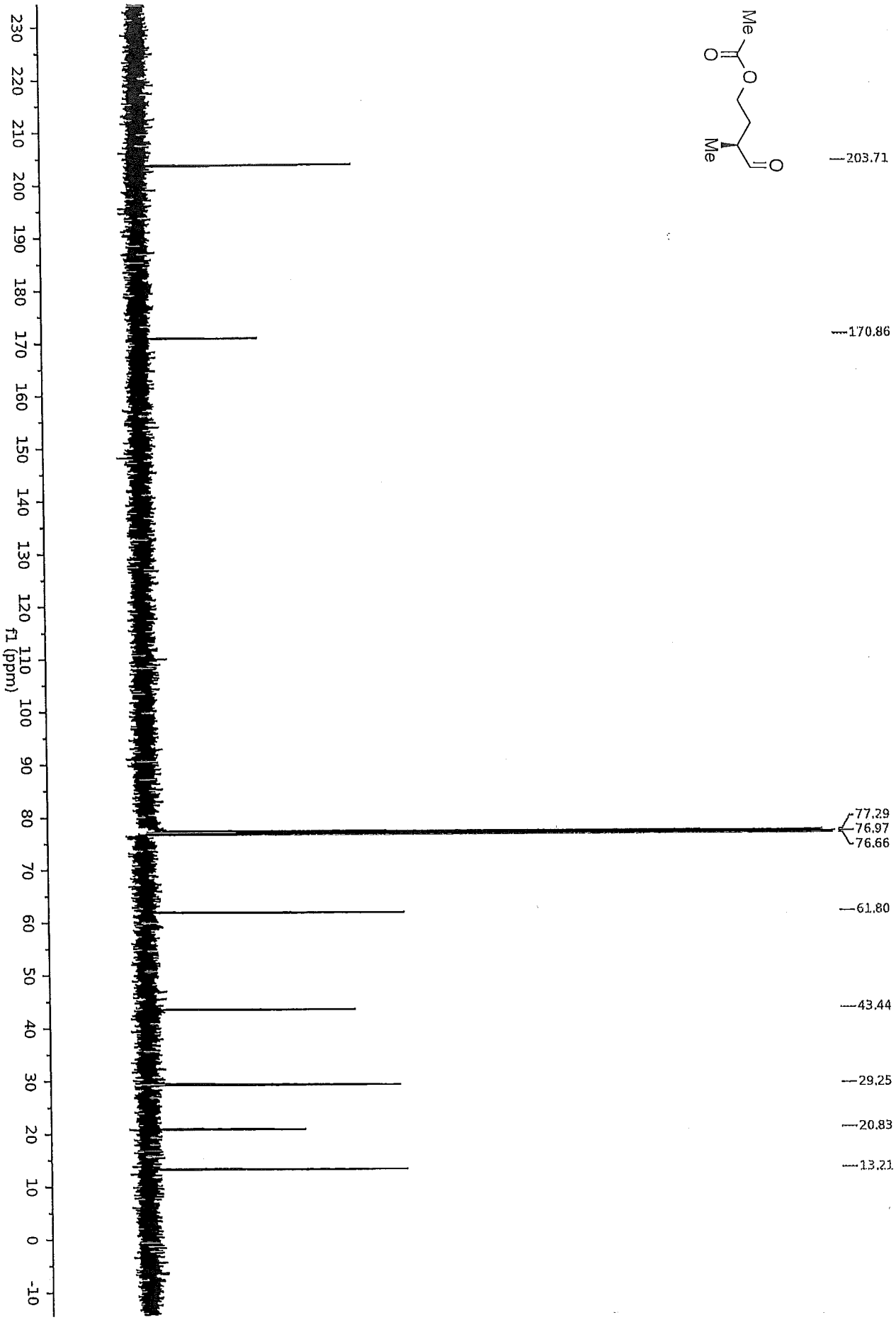
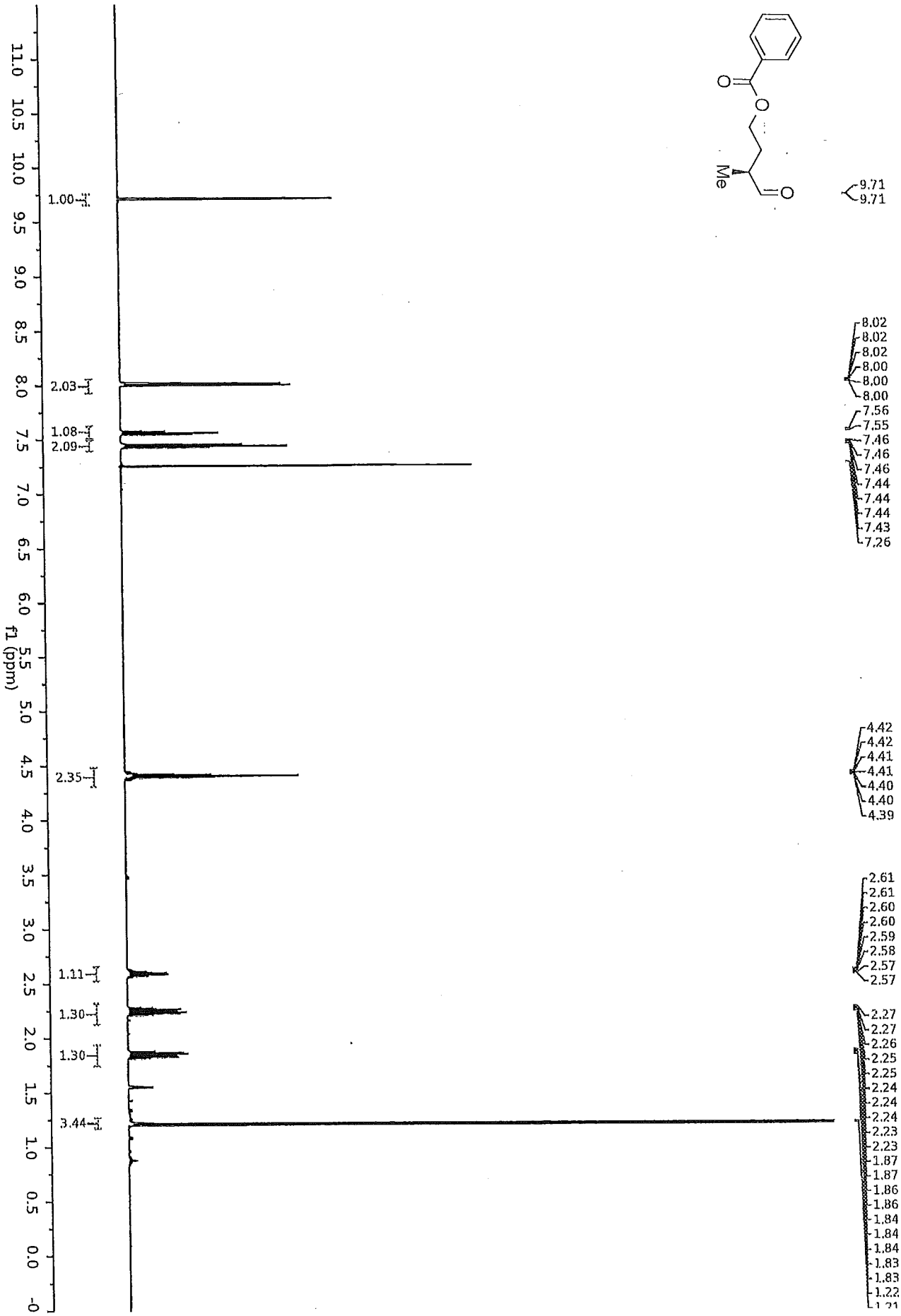
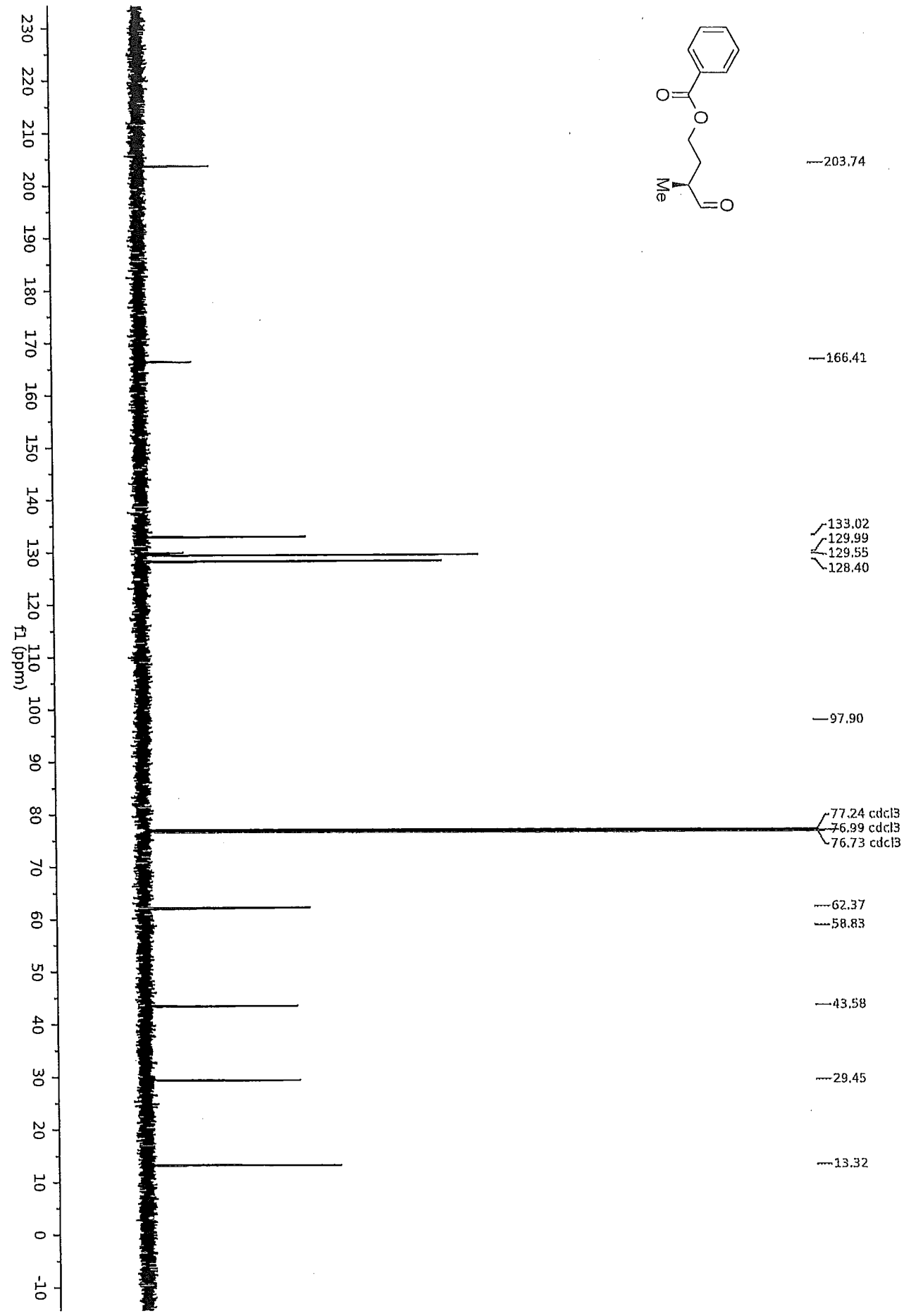
1.18
1.18
1.17
1.16
1.16
1.16


Me
O
O
O
202.48
139.00
138.98
127.83
127.70
108.86
77.22 cdcl3
77.01 cdcl3
76.80 cdcl3
73.26
72.83
51.08
9.44
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


Me
O
O
O
Me
O
9.65
9.65
7.26
4.16
4.16
4.15
4.15
4.15
4.14
4.14
4.14
4.14
4.13
4.13
4.13
4.12
2.50
2.50
2.49
2.49
2.48
2.48
2.17
2.17
2.10
2.09
2.07
2.05
2.04
2.04
2.04
2.04
1.73
1.71
1.70
1.17
1.17
1.16
1.16
1.16
1.15
1.15
1.00
2.24
1.03
1.13
2.95
1.20
3.21
f1 (ppm)
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0


Me
O
O
Me
O
203.71
170.86
77.29
76.97
76.66
61.80
43.44
29.25
20.83
13.21
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


f1 (ppm)
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
1.00
2.03
1.08
2.09
2.35
1.11
1.30
1.30
3.44
Me
O
O
O
O
9.71
9.71
8.02
8.02
8.02
8.00
8.00
8.00
7.56
7.55
7.46
7.46
7.46
7.44
7.44
7.44
7.43
7.26
4.42
4.42
4.41
4.41
4.40
4.40
4.39
2.61
2.61
2.60
2.60
2.59
2.58
2.57
2.57
2.27
2.27
2.26
2.25
2.25
2.24
2.24
2.24
2.23
2.23
1.87
1.87
1.86
1.86
1.84
1.84
1.84
1.83
1.83
1.22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129.55
128.40
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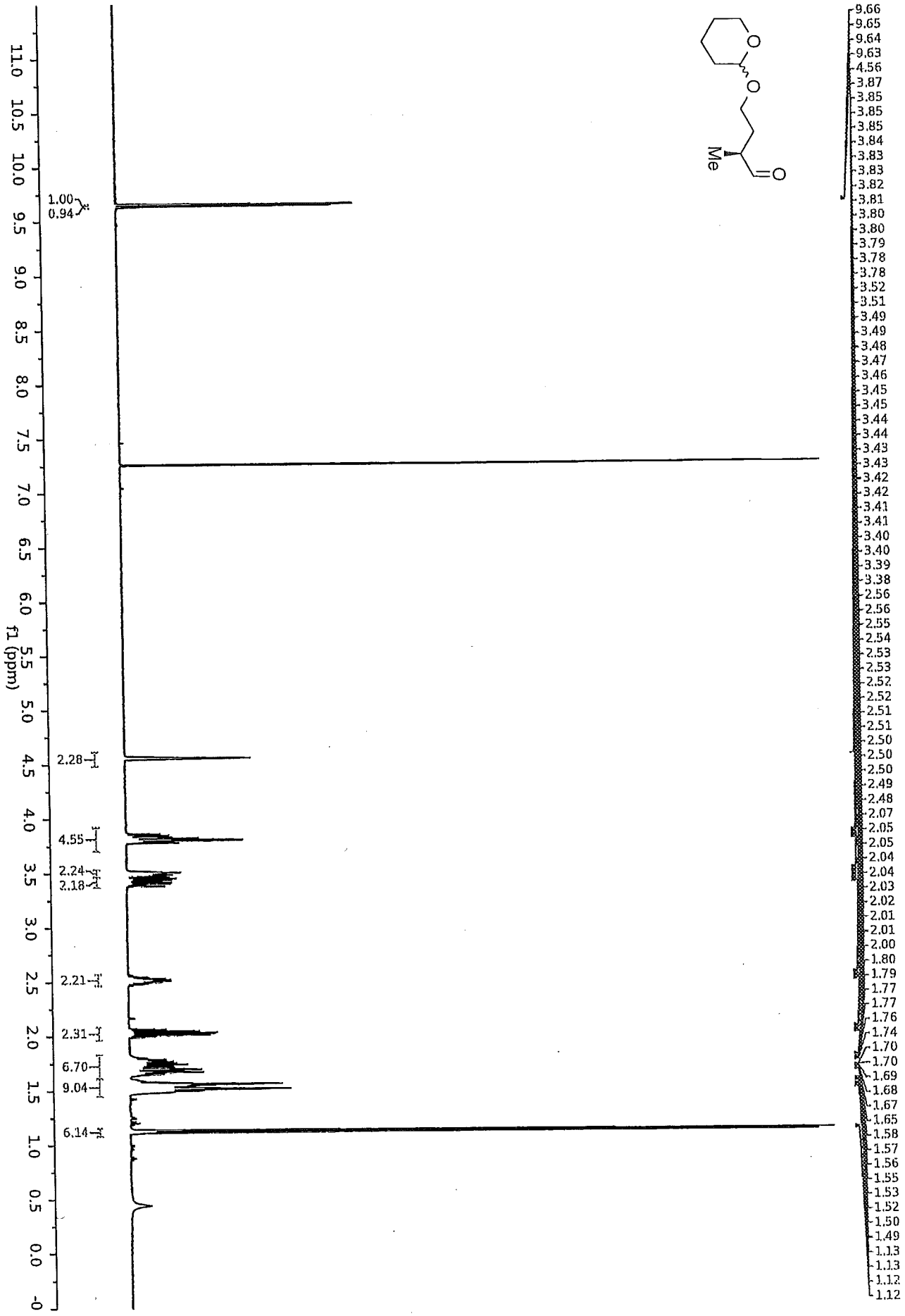
43.58
29.45
13.32
f1 (ppm)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4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
1.00
0.94
2.28
4.55
2.24
2.18
2.21
2.31
6.70
9.04
6.14
Me
O
O
O
9.66
9.65
9.64
9.63
4.56
3.87
3.85
3.85
3.85
3.84
3.83
3.83
3.82
3.81
3.80
3.80
3.79
3.78
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3.46
3.45
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3.43
3.42
3.42
3.41
3.41
3.40
3.40
3.39
3.38
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2.50
2.50
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2.05
2.05
2.04
2.04
2.03
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2.01
2.01
2.00
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1.77
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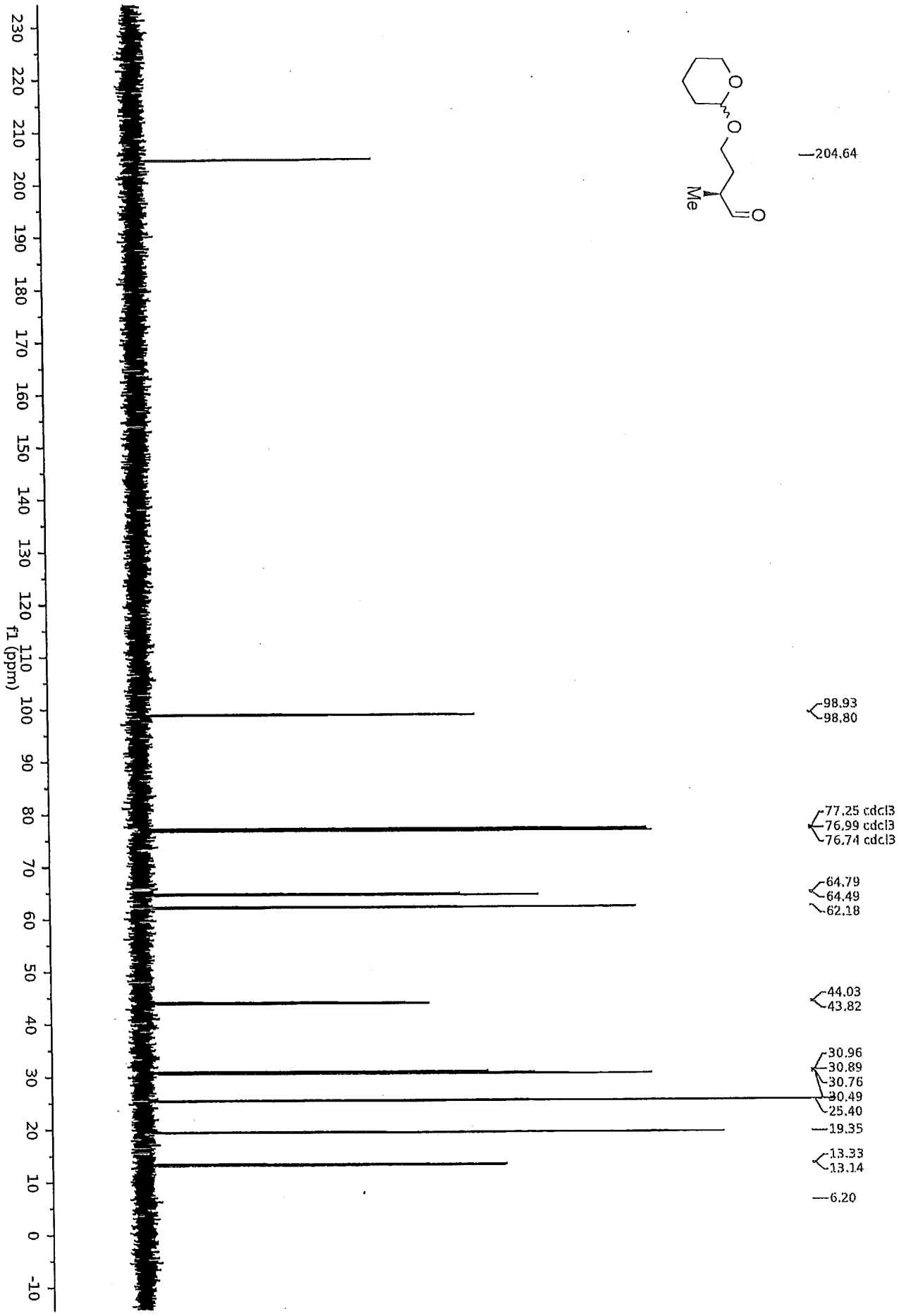
1.12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98.80
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76.74 cdcl3
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64.49
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43.82
30.96
30.89
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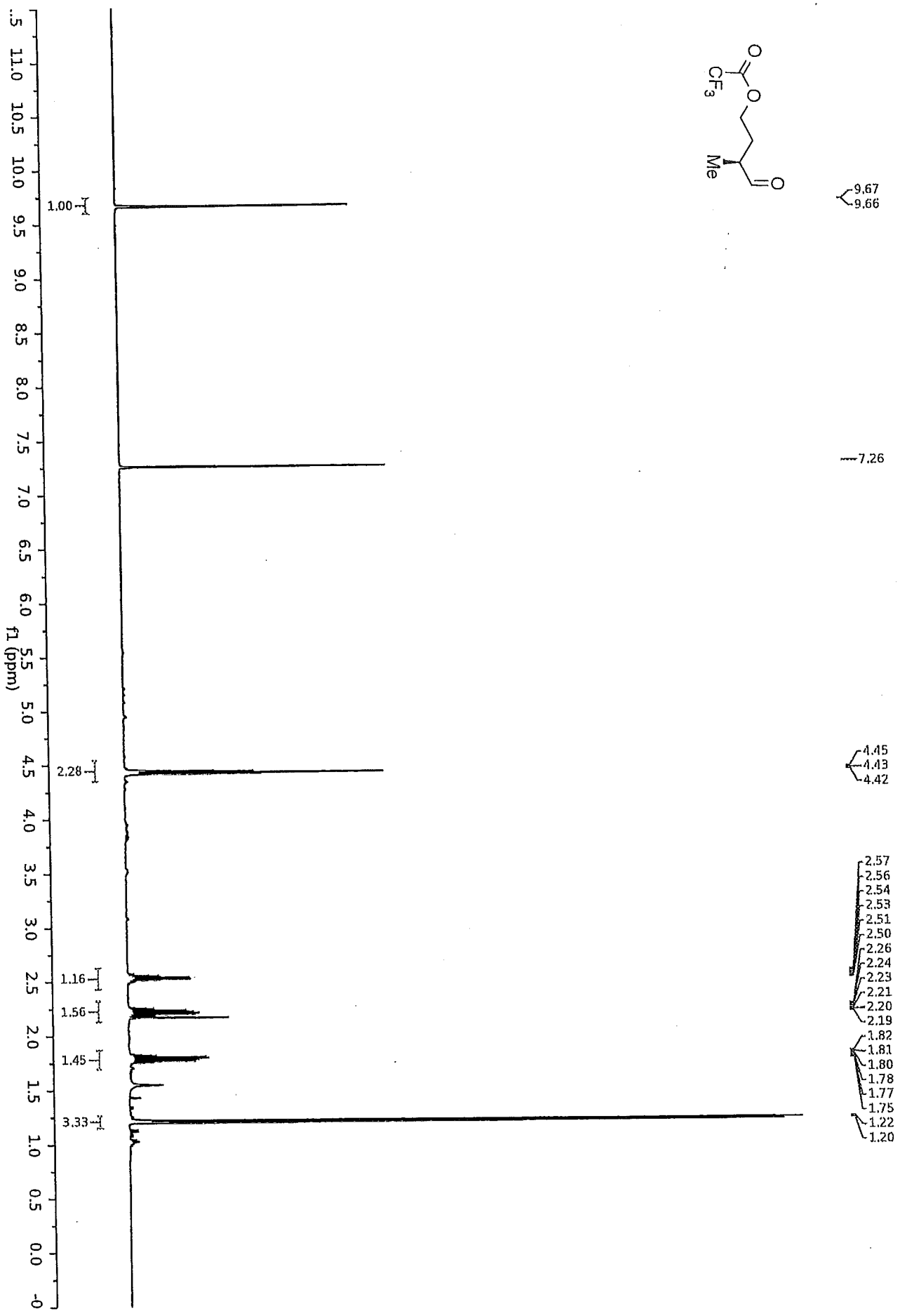
30.49
25.40
19.35
13.33
13.14
6.20
Me
O
O
O
f1 (ppm)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4.42
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2.56
2.54
2.53
2.51
2.50
2.26
2.24
2.23
2.21
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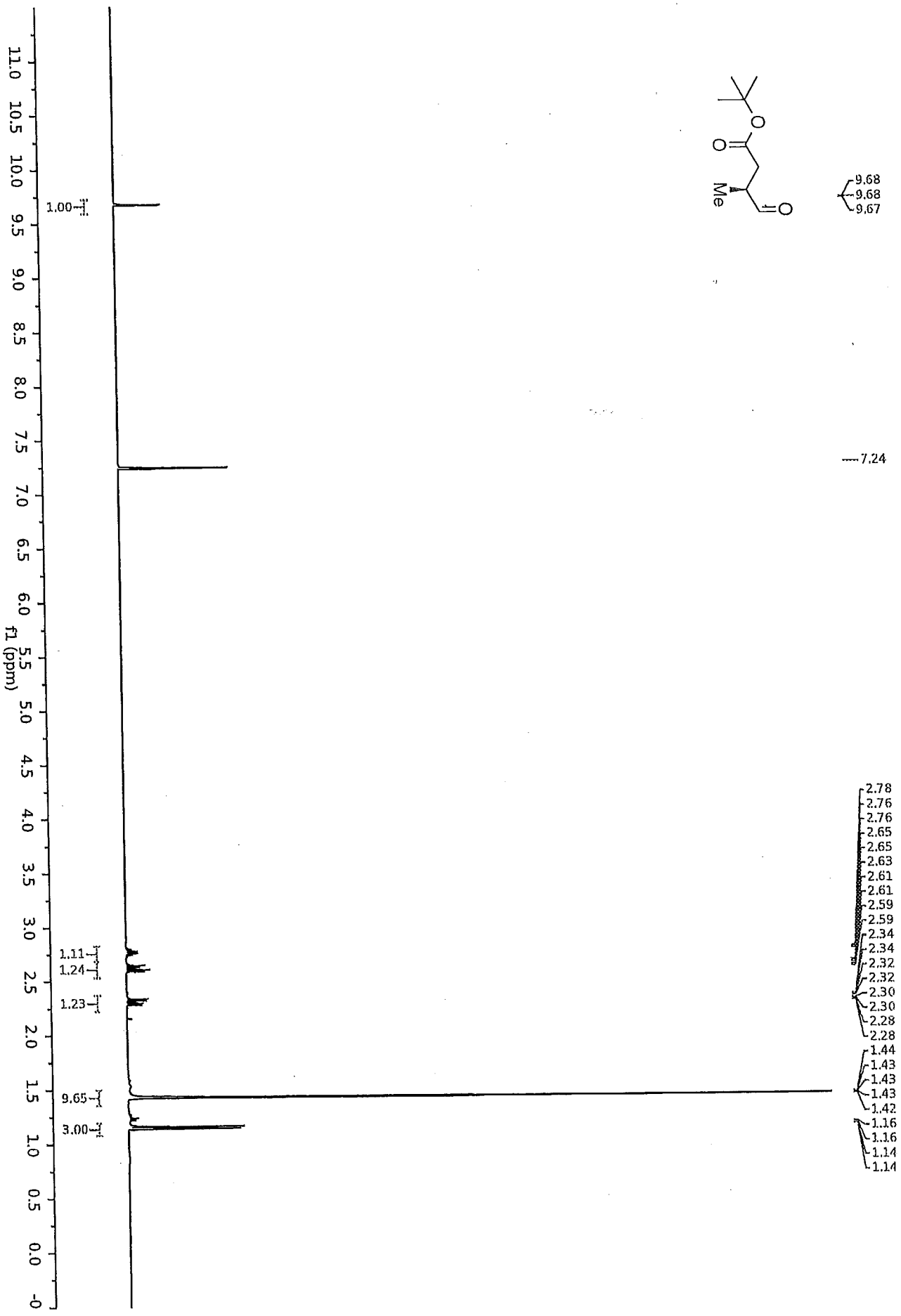
Me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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
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1.11
1.24
1.23
9.65
3.00
O
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Me
O
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9.68
9.67
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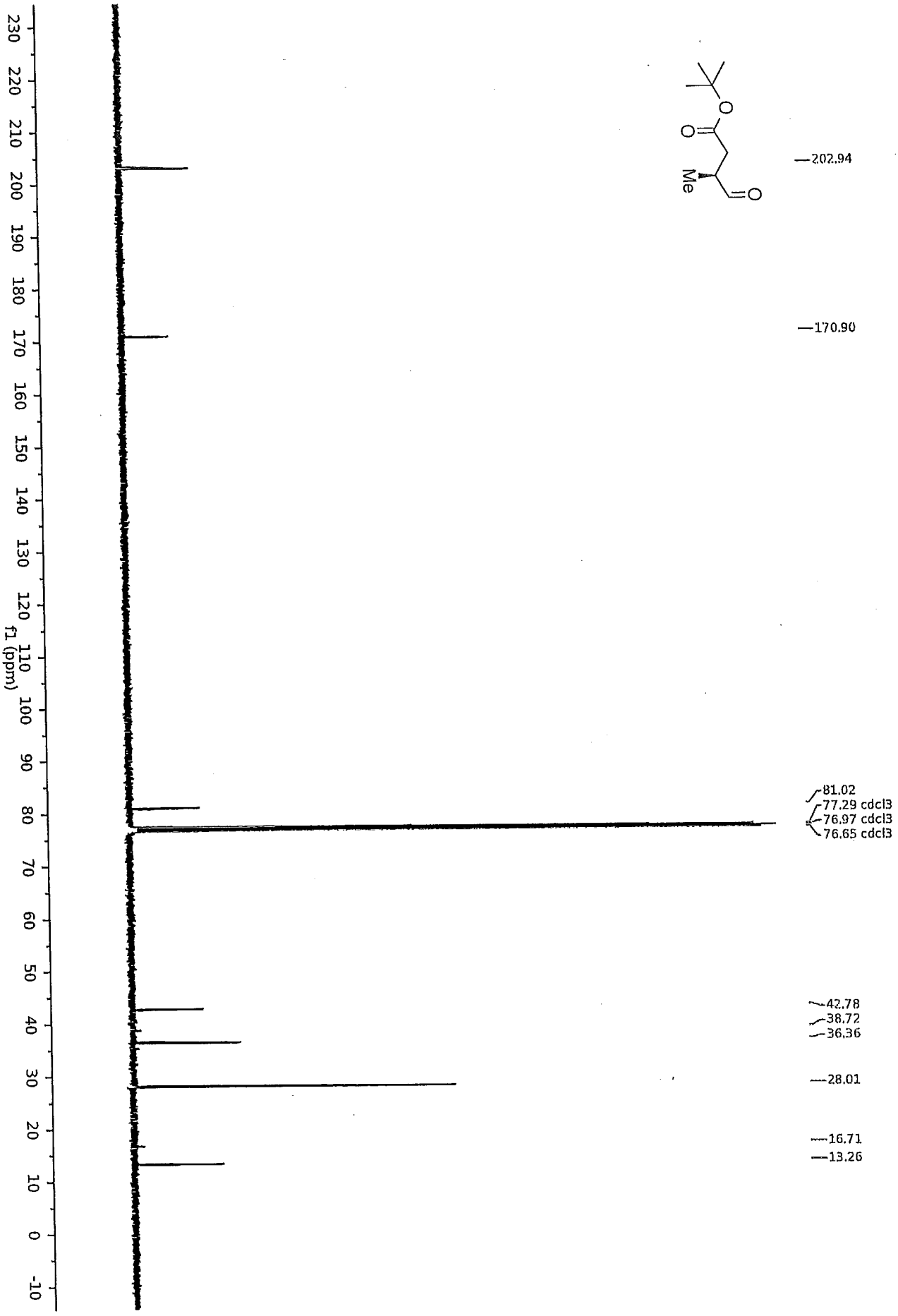
1.14
1.14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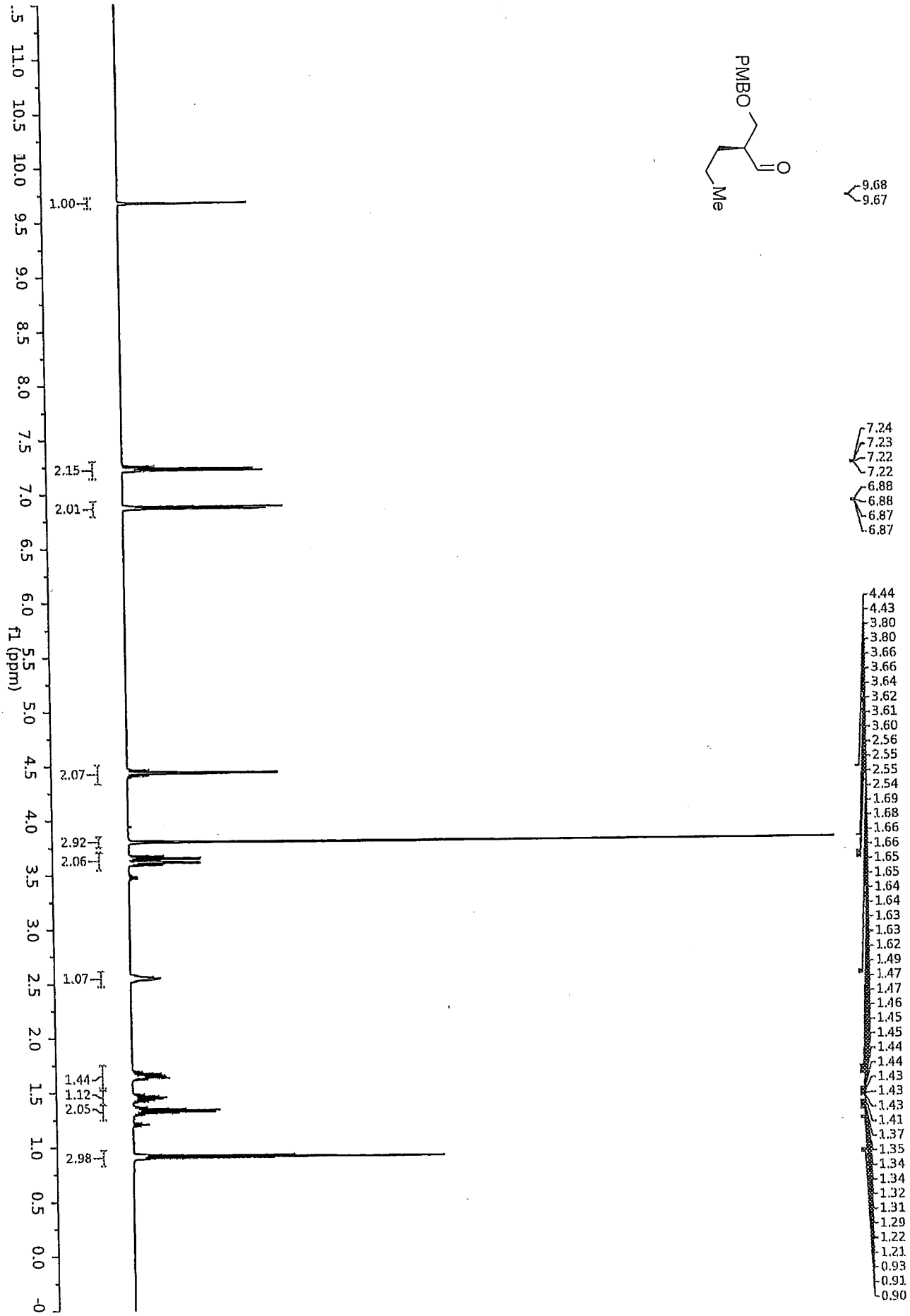
f1 (ppm)


PMBO
Me
O
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7.22
7.22
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6.88
6.87
6.87
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3.80
3.80
3.66
3.66
3.64
3.62
3.61
3.60
2.56
2.55
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1.43
1.41
1.37
1.35
1.34
1.34
1.32
1.31
1.29
1.22
1.21
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0.91
0.90
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2.15
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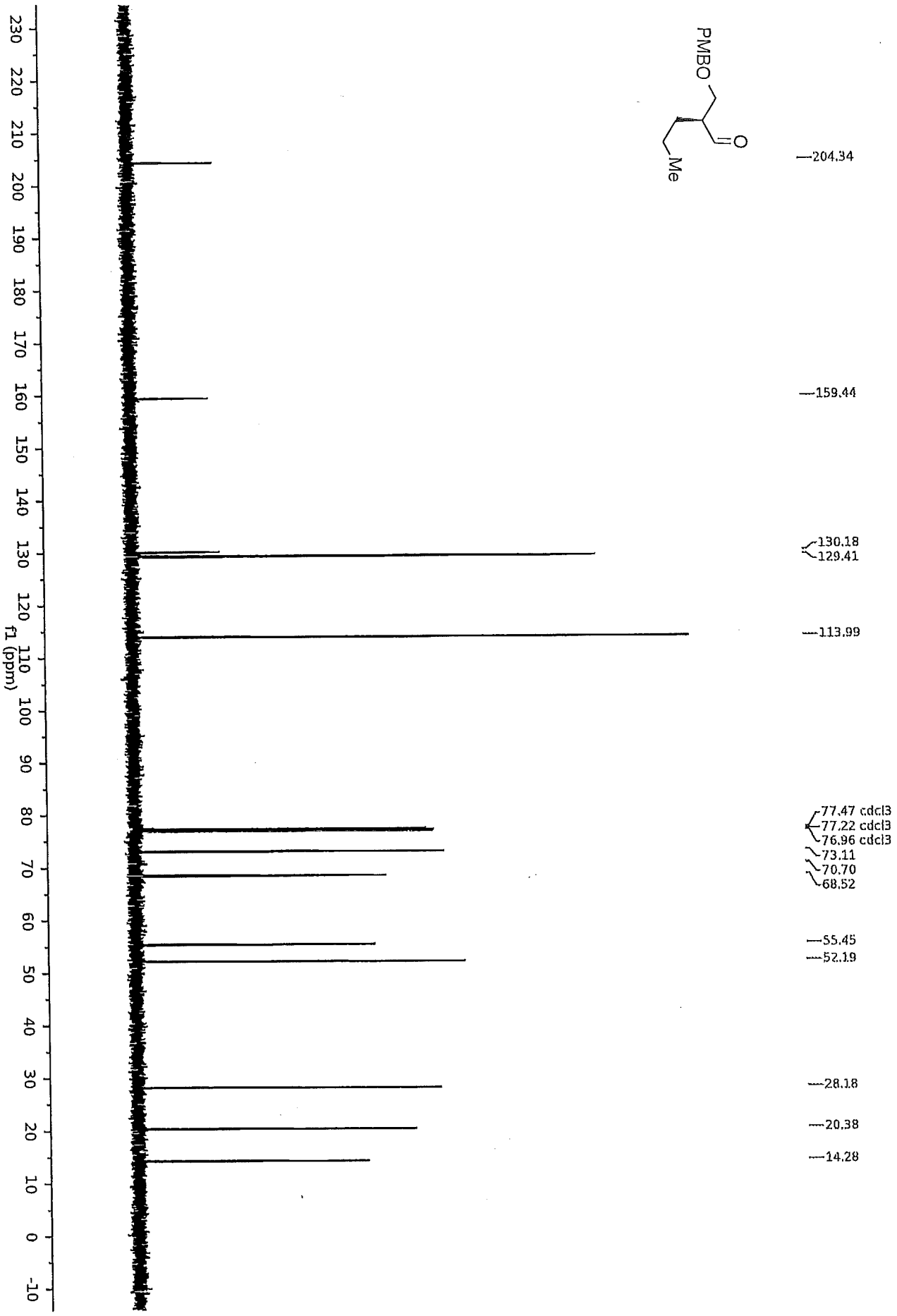
2.07
2.92
2.06
1.07
1.44
1.12
2.05
2.98
f1 (ppm)


PMBO
O
Me
204.34
159.44
130.18
129.41
113.99
77.47 cdcl3
77.22 cdcl3
76.96 cdcl3
73.11
70.70
68.52
55.45
52.19
28.18
20.38
14.28
f1 (ppm)

# Chapter 3

# Desymmetrization of Cyclic Sulfates via Enantioselective Kumada-Corriu Coupling

## 3.1 Metal-Catalyzed Desymmetrization Reactions[1]

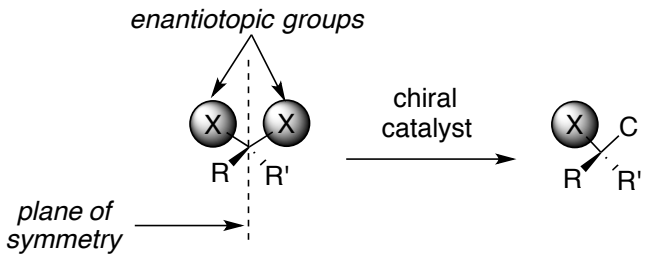
The formation of new stereocenters by carbon-carbon bond formation is most commonly achieved *via* asymmetric bond formation at the new stereogenic center.[2] However, desymmetrization reactions offer an alternate approach that separates the newly forming stereocenter from the site of carbon-carbon bond formation. In a desymmetrization, a chiral species is used to differentiate between two enantiotopic groups of a readily-available prochiral compound (Scheme 3.1). The introduction of this chapter will focus on detailing previously developed metal-catalyzed desymmetrization reactions that proceed via carbon-carbon bond formation. Though a substantial number

[1] For reviews on desymmetrization reactions see: (a) Magnuson, S. R. *Tetrahedron*, **1995**, *51*, 2167. (b)Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron*, **1996**, *52*, 14361. (c) Maertnes, G.; Menard, M.-A.; Canesi, S. *Synthesis*, **2014**, *46*, 1573. (d) Peterson, K. S. *Tetrahedron Lett.* **2015**, *56*, 6523. (e) Zeng, P.-X.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330. (e) Rovis, T. *Recent Advances in Catalytic Asymmetric Desymmetrization Reactions, In New Frontiers in Asymmetric Catalysis*; Mikami, K.; Lautens, M., Eds.; Wiley: New York, 2007, 275–312.

[2] For reviews and books on asymmetric C-C bond forming reactions see: (a) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587. (b) Douglas, C. J.; Overman, L. E. *PNAS,* **2004**, *101*, 5363. (c) Jacobsen, E. N., Pfaltz, A. & Yamamoto, H. (eds) *Comprehensive Asymmetric Catalysis*: Suppl. 2. (Springer-Verlag, 2004). (d) Noyori, R. (eds) *Asymmetric Catalysis in Organic Synthesis*. (John Wiley & Sons, 1994).

of useful desymmetrization reactions utilize organocatalysts or enzymes, those examples will not be discussed here.[3]

**Scheme 3.1: Desymmetrization of Prochiral Compounds**




### 3.1.1 *Desymmetrization of Prochiral Biselectrophiles*

#### *3.1.1.1 Desymmetrization of meso-Anhydrides*

The desymmetrization of *meso*-cyclic anhydrides has been extensively studied by Rovis and co-workers over the past 15 years.[4] In 2002, the first example of an asymmetric alkylative cross-coupling of cyclic anhydrides was presented by Rovis and co-workers.[5] Desymmetrization of anhydride **3.1** with $ZnEt_2$ in the presence of $Ni(acac)_2$ and Phox ligand **L3.1** yields ketoacid **3.3** in 79% ee and 85% yield (Scheme 3.2). Addition of electron-deficient olefins, such as **3.2**, to cross-coupling reactions is proposed to increase the rate

[3] For reviews on organocatalyzed and enzymatic desymmetrizations see: (a) Diaz-de-Villegas, M. D.; Galvez, J. A.; Badorrey, R.; Lopez-Ram-de-Viu, M. P. *Chem. Eur. J.* **2012**, *18*, 13290. (b) de-Villegas, M. D.; Galvez, J. A.; Etayo, P.; Badorrey, R.; Lopez-Ram-de-Viu, M. P. *Chem. Soc. Rev.* **2011**, *40*, 5564. (c) Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev*. **2007**, *107*, 5683. (d) Palomo, J. M.; Cabrera, Z. *Curr. Org. Synth.* **2012**, *9*, 791.

[4] For a review on asymmetric reactions of anhydrides see: Johnson, J.; Rovis, R. *Acc. Chem. Res.* **2007**, *41*, 327.

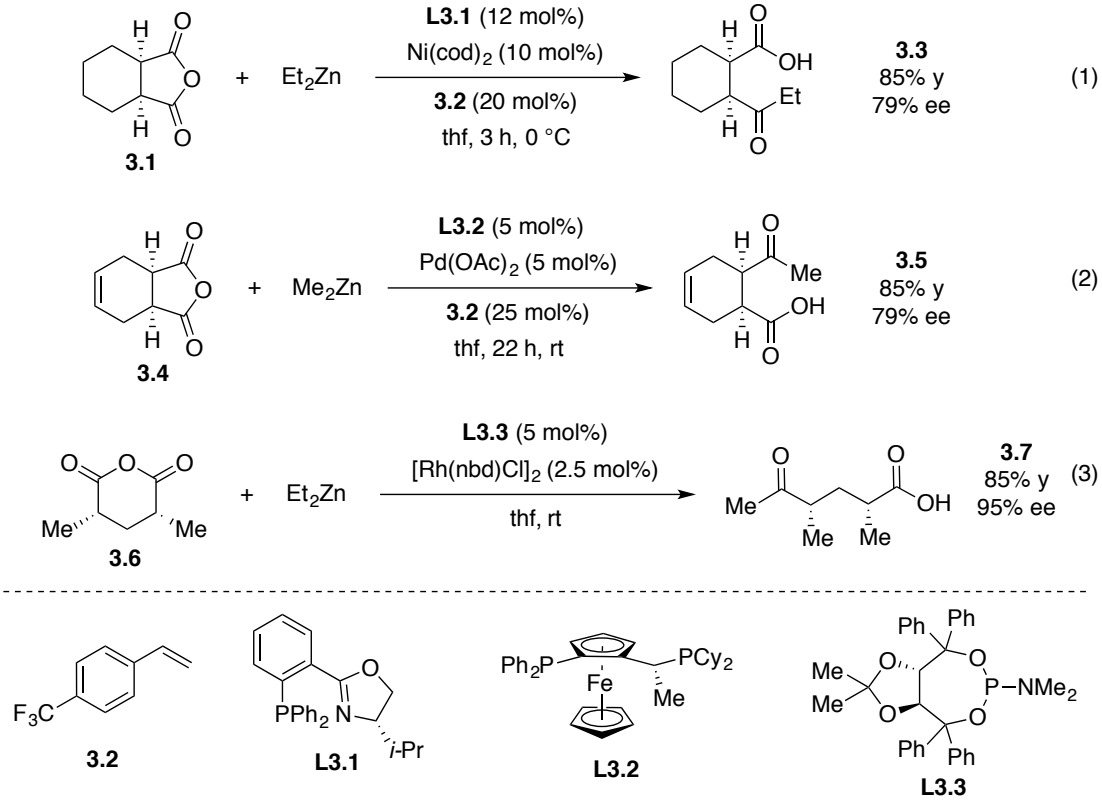
[5] Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc*. **2002**, *124*, 174.

by facilitating reductive elimination. However, in this case the additive was found to have a significant impact on the enantioselectivity of the reaction, with ketoacid **3.3** being formed with only 4% ee in the absence of **3.2**.[6] Kinetic studies revealed that oxidative addition is the rate-determining step of the process and addition of **3.2** accelerates the rate of this step, rather than reductive elimination. Due to issues in expanding the scope of the Ni-catalyzed desymmetrization, Rovis and Bercot developed a Pd-catalyzed Negishi coupling of succinic anhydrides **3.4** (Scheme 3.2, eq. 2). This method could be applied to both $Ar_2Zn$ and $Et_2Zn$ nucleophiles but zinc halides salts were not tolerated (RZnX). In 2007, Cook and Rovis were able to use a Rh/**L3.3** catalyst system in the desymmetrization of glutaric acid derived ahydrides **3.6** which gave high yields and enantioselectivities for both alkyl zinc halides and dialkylzinc nucleophiles (Scheme 3.2, eq. 3).[7]

[6] For previous studies on electron-deficient olefin in Ni-cross-couplings see: (a) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed*. **1998**, *37*, 2387. (b) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem*. **1999**, *64*, 3544.

[7] Cook, M. J.; Rovis, T. *J. Am. Chem. Soc*. **2007**, *129*, 9302.

**Scheme 3.2: Desymmetrization of *meso*-Anhydrides by Rovis and Co-Workers**



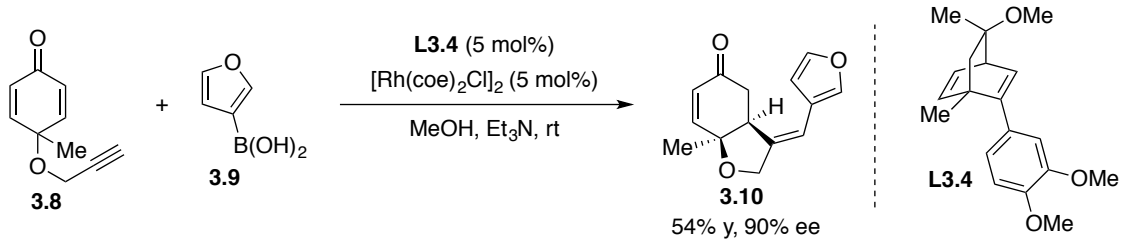

### *3.1.1.2 Desymmetrization of Dienones*

In addition to the desymmetrization of *meso*-anhydrides, several methods have been developed for the desymmetrization of prochiral dienones. Though most of these methods rely on organocatalysts, there are a few transition-metal catalyzed desymmetrizations of dienones reported.[8] One strategy used to desymmetrize alkynyl substituted dienones involves carbometalation of the alkyne followed by 1,4-addition. Lautens and co-workers have developed the asymmetric Rh-catalyzed arylative

[8] For a review on desymmetrizations of prochiral dienone systems see: Maeterns, G.; Menard, M.-A.; Canesi, S. *Synthesis*, **2004**, *46*, 1573.

cyclization of dienone **3.8**, which proceeds in the presence of chiral diene ligand **L3.4** with high enantioselectivity and moderate yield (Scheme 3.3).[9]

**Scheme 3.3: Rh-Catlayzed Arylative Cyclization of Dienones by Lautens**

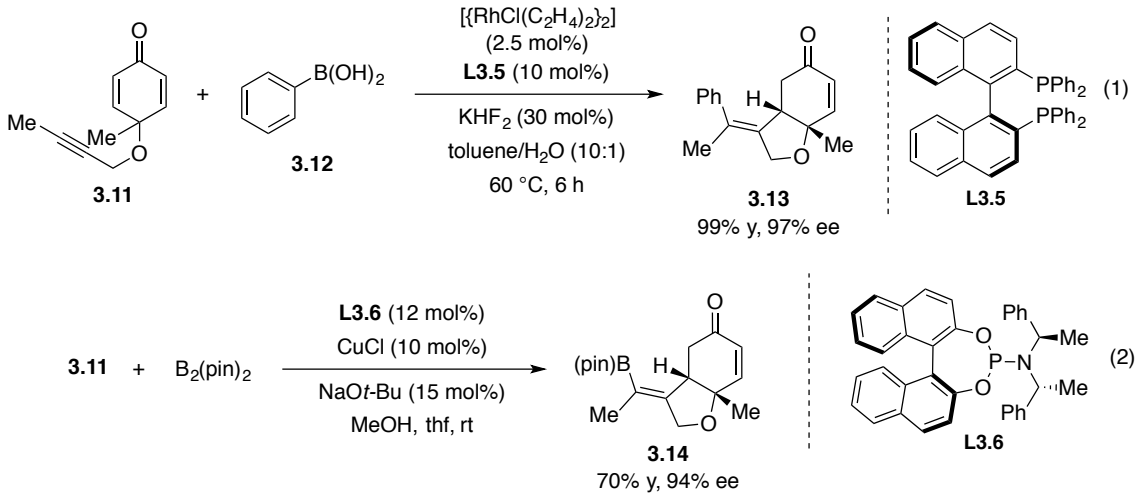



The same year Lin and co-workers presented a similar Rh-catalyzed asymmetric arylative cyclization of symmetric cyclic dienones with boronic acids.[10] The use of $[\{RhCl(C_2H_4)_2\}_2]$ with **L3.5** in the presence of catalytic $KHF_2$ efficiently converts cyclohexadienone **3.11** into hydrobenzofuran **3.13** (Scheme 3.4, eq. 1). In previous work on Rh-catalyzed conjugate additions, Lin and co-workers found that addition of $KHF_2$ in toluene/water mixtures was critical for high yields.[11] After experimental evidence ruled out *in situ* formation of tetrafluoroborate salts, the authors propose that fluoride ions play a role in stabilizing catalytic intermediates. Lin and co-workers later developed a Cu-catalyzed borylative desymmetrization of cyclic dienones.[12] Cyclohexadienone **3.11** is

[9] Keilitz, J.; Newman, S. G.; Lautens, M. *Org. Lett.* **2013**, *15,* 1148.
[10] He, Z.-T.; Tian, B.; Fukui, Y.; Tong, X.; Tian, P.; Lin, G.-Q. *Angew. Chem. Int. Ed.* **2013**, *52*, 5314.
[11] Wang, Z.-Q.; Feng, C.-G.; Zhang, S. S.; Zu, M.-H.; Lin, G.-Q. *Angew. Chem. Int. Ed.* **2010**, *49*, 5780.
[12] Liu, P.; Fukui, Y.; Tian, P.; He, Z.-T.; Sun, C.-Y.; Wu, N.- Y.; Lin, G.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 11700.

converted to **3.14** in the presence of CuCl, **L3.6** and $B_2(pin)_2$ in high yield and enantioselectivity (Scheme 3.4, eq. 2).

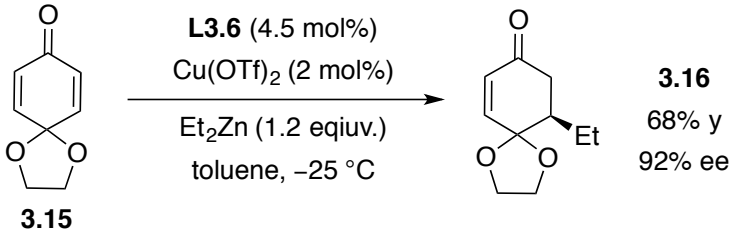
**Scheme 3.4: Desymmetrizations of Symmetric Cyclic Dienones by Lin and Co-Workers**




Disubstituted cyclic dienones have also been efficiently desymmetrized *via* asymmetric copper-catalyzed conjugate additions of organozinc reagents. In 1999, Feringa and co-workers reported that symmetric cyclic dienone **3.15** in the presence of $Cu(OTf)_2$ and phosphoramidite ligand **L3.6** could efficiently undergo enantioselective 1,4-addition with $Et_2Zn$ (Scheme 3.5). This method is limited to substrates with oxygen substituents at the 4-position of the dienone. Thompson and co-workers broadened the scope of the reaction by developing a similar rhodium-catalyzed desymmetrization with organozinc reagents.[13]

[13] (a) Konkol, L. C.; Guo, F.; Sarjeant, A. A.; Thompson, R. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 9931. (b) Guo, F.; Konkol, L. C.; Thompson, R. J. *J. Am. Chem. Soc.* **2011**, *133*, 18.

**Scheme 3.5: Desymmetrizations of Symmetric Cyclic Dienones by Feringa and Co-Workers**

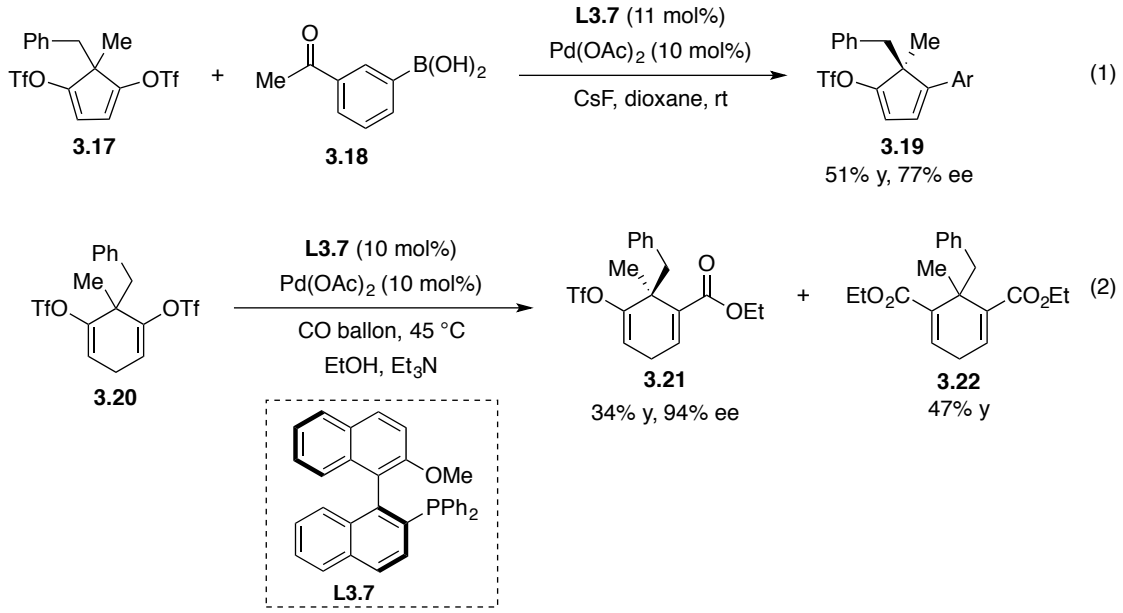



### *3.1.1.3 Desymmetrizations of meso-Electrophiles via Cross-Coupling*

In 2004, Willis and co-workers developed a unique desymmetrization of prochiral ditriflates through an asymmetric palladium-catalyzed cross-coupling reaction.[14] Asymmetric Suzuki coupling of **3.17** with arylboronic acid **3.18** in the presence of $Pd(OAc)_2$ with monophosphine **L3.7**, yields the desired monotriflate **3.19** in moderate yield and enantioselectivity (Scheme 3.6, eq. 1). Later this group was able to achieve the desymmetrization of similar ditriflates through a asymmetric carbonylative cross-coupling under mild conditions with a similar catalyst system (Scheme 3.6, eq. 2).[15] The yields in this case were low due to formation of undesired diester **3.22** from biscoupling.

[14] Willis, M. C.; Powell, L. H. W.; Claverie, C. K.; Watson, S. J. *Ang. Chem. Int. Ed.* **2004**, *43*, 1249.
[15] Byrne, S. J.; Fletcher, A. J.; Hebeisen, P.; Willis, M. C. *Org. Biomol. Chem.* **2010**, *8*, 758.

**Scheme 3.6: Desymmetrization of Ditriflates by Willis and Co-Workers**

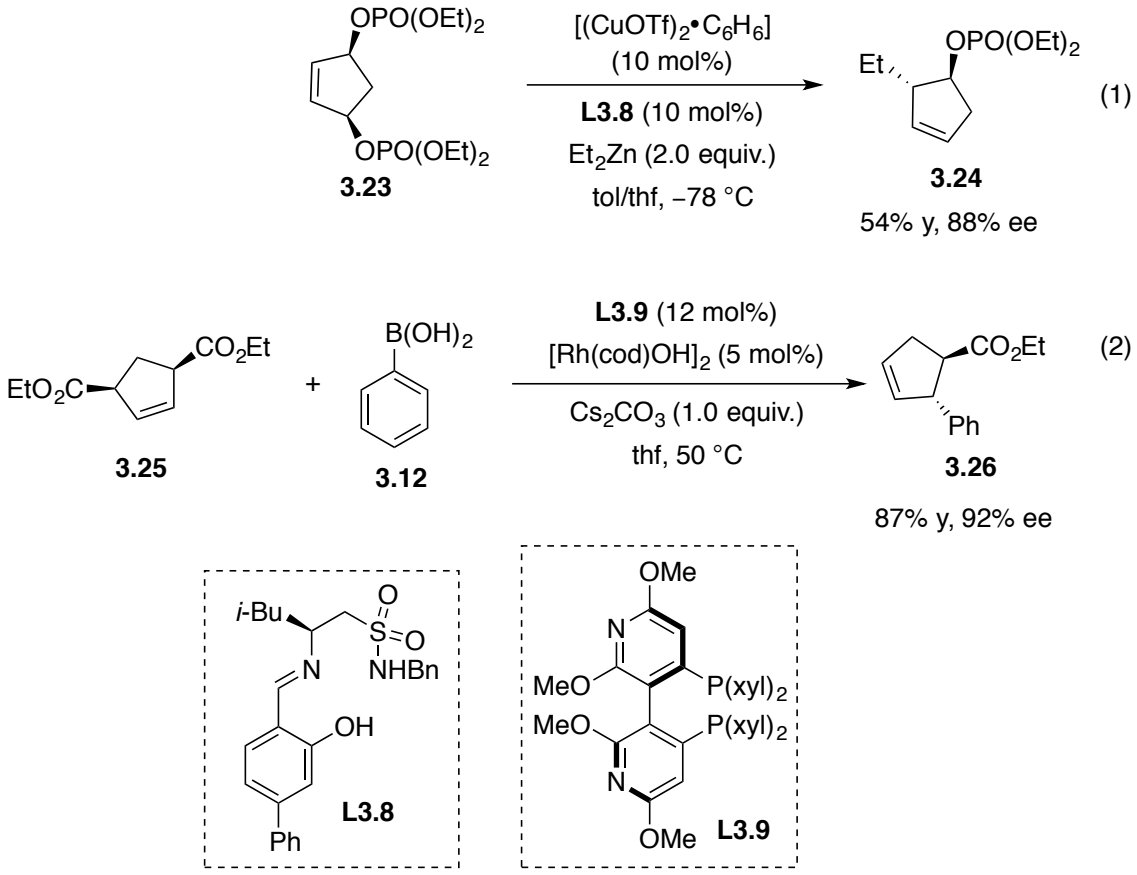



*meso*-Cyclic allylic alcohol derivatives have also been used as substrates for desymmetrization reactions which proceed *via* cross-coupling. In 2003, Gennari and co-workers developed the desymmetrization of simple *meso*-cyclic allylic bis(phosphates).[16] Addition of $Et_2Zn$ to allylic bisphosphate **3.23** in the presence of catalytic $Cu(OTf)_2$ and chiral Schiff base ligand **L3.8**, proceeds smoothly to give **3.24** in high yield and enantioselectivity (Scheme 3.7, eq. 1). The desymmetrization can also be applied to six- and seven-membered ring *meso*-allylic bis(phosphates).[17] The asymmetric Suzuki coupling of cyclic allylic bis(carbonates) was developed by Lautens and co-workers.[18] Bidentate phosphine **L3.9** in combination with a rhodium catalyst catalyzes the

[16] Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 234.
[17] Piarulli, U.; Daubos, P.; Claverie, C.; Monti, C.; Gennari, C. *Eur. J. Org. Chem.* **2005**, *2005*, 895.
[18] Menard, F.; Chapman, T. M.; Dockendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569.

asymmetric Suzuki coupling of prochiral bis(carbonate) **3.25** with arylboronic acid **3.12** (Scheme 3.7, eq. 2).

**Scheme 3.7: Desymmetrization of *meso*-Cyclic Allylic Alcohol Derivatives**

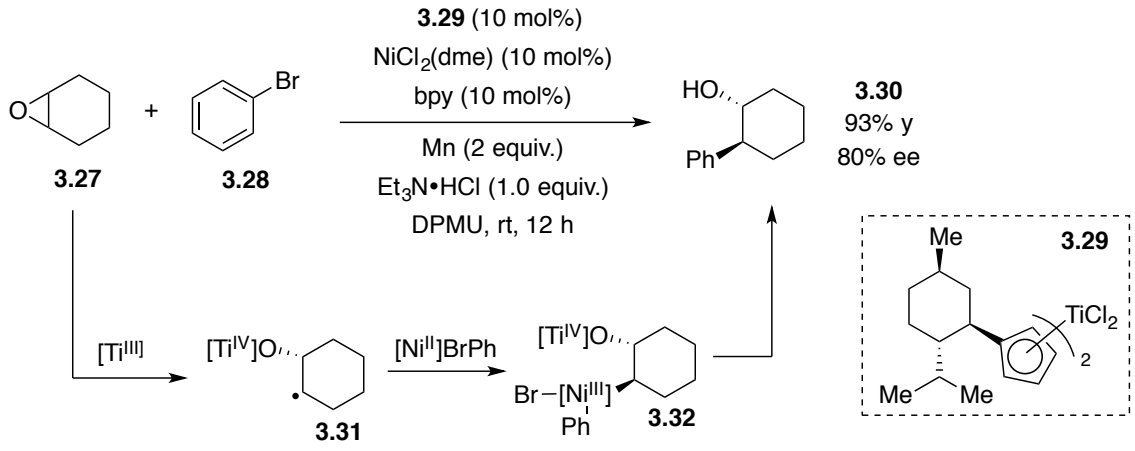



More recently, Zhao and Weix have designed a desymmetrization of *meso*-epoxides which proceeds through an asymmetric cross-coupling of aryl halides (Scheme 3.8).[19] Asymmetric ring-opening of *meso*-epoxide **3.27** with chiral-titanium **3.29** results in

[19] Zhou, Y.; Weix, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 3237.

radical species **3.31**. Oxidative addition of **3.31** to an achiral arylnickel(II) species followed by reductive elimination yields **3.30** in high yield and enantioselectivity.

**Scheme 3.8: Asymmetric Cross-Coupling of *meso*-Epoxides by Weix and Zhou.**




### *3.1.2 Desymmetrization of Prochiral Bisnucleophiles*

#### *3.1.2.1 Desymmetrization by Olefin Metathesis*

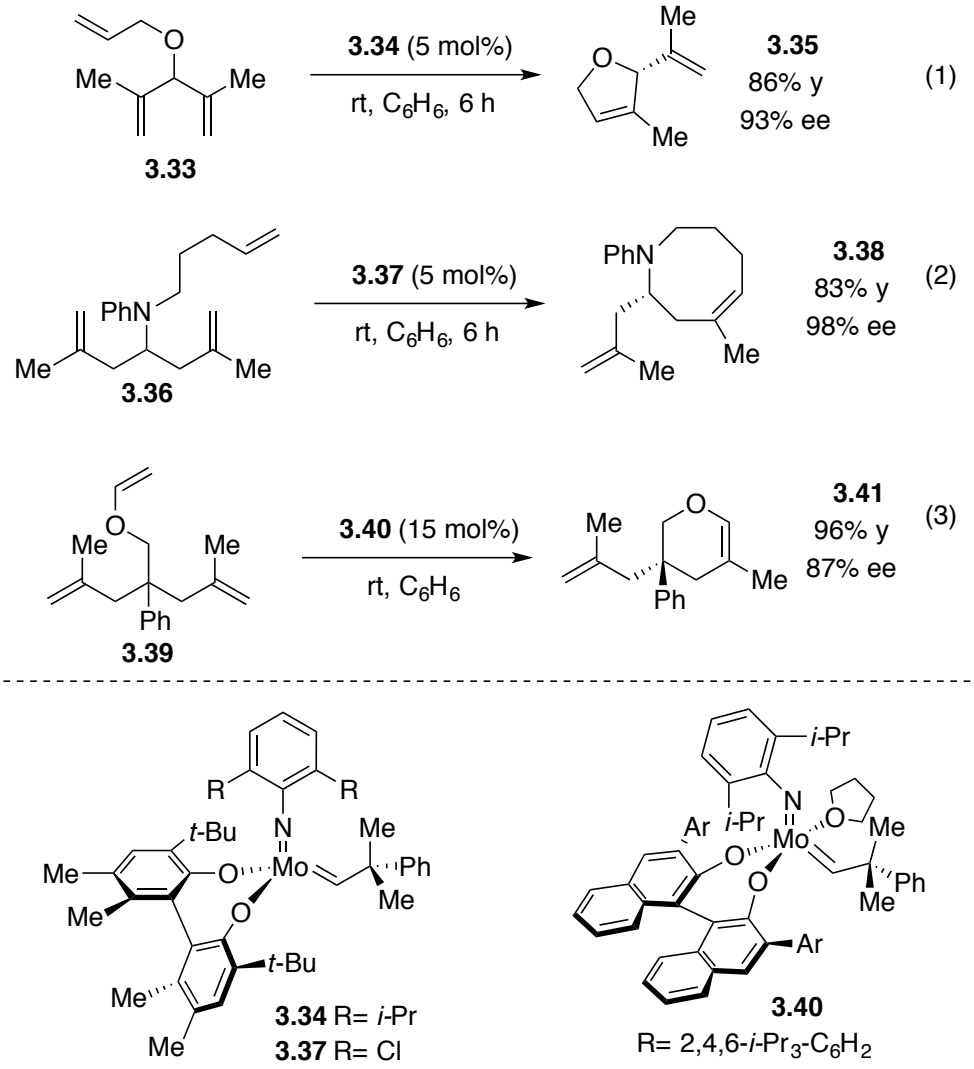
Catalytic enantioselective ring-closing metathesis (RCM) of trienes is also a well-developed desymmetrization strategy. Early examples of desymmetrization reaction via RCM utilized chiral Mo-catalyst (**3.34** and **3.37**), developed by Hoveyda and Schrock.[20] These catalysts can efficiently desymmetrize a variety of achiral trienes to form optically

[20] (a) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4014.(b) Hoveyda, A. H.; Schock, R. R. *Chem. Eur. J.* **2001**, *7*, 945.

pure cyclic ethers[21] and amines[22] with low catalyst loadings (Scheme 3.9, eq. 1 and 2). In 2006, Hoveyda and co-workers extended this method to the desymmetrization of trienes to form all-carbon quaternary centers. In the presence of 15 mol% of Mo-complex **3.40**, achiral triene **3.39** is efficiently converted into six-membered pyran derivative **3.41** (Scheme 3.9, eq. 3). Desymmetrization via RCM is not limited to Mo-catalysts; Ru- and W-catalysts have also been used in asymmetric RCM.[23]

[21] (a) Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahderon Lett.* **2000**, *41*, 9553. (b) La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem Soc.* **1998**, *120*, 9720.
[22] Sattely, E. S.; Cortez, G. A.; Moebuis, D. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 8526.
[23] (a) Zhao, Y.; Hoveyda, A. H.; Schrock, R. R. *Org. Lett.* **2011**, *13*, 784. (b) Stenne, B.; Timperio, J.; Savoie, J.; Dudding, T.; Collings, S. K. *Org. Lett.* **2010**, *12*, 2032. (c) Fournier, P.-A.; Savoie, J.; Stenne, B.; Bedard, M.; Grandbois, A.; Collins, S. K. *Chem. Eur. J.* **2008**, *14*, 8690. (d) Fourneir, P.-A.; Collins, S. K. *Organometallics* **2007**, *26*, 2945. (e) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225.

**Scheme 3.9: Desymmetrization of Achiral Trienes *via* Ring-Closing Metathesis**

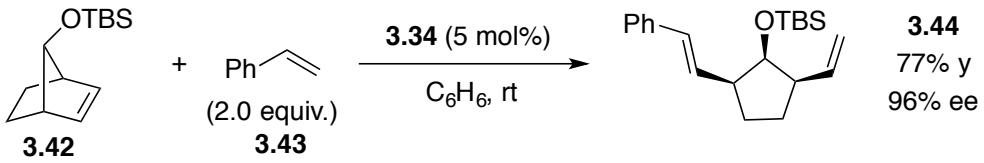



In addition to desymmetrizations by ring closing metathesis, tandem asymmetric ring-opening/cross-metathesis can efficiently achieve the desymmetrization of strained *meso*-cyclic alkenes.[24] For example, norbornyl TBS ether **3.42** under goes ring-

[24] For a review on ROM/CM see: La, D. S.; Sattely, E. S.; Ford, J. G.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 7767.

opening/cross-metathesis (ROCM) with **3.43** in the presence of Mo-cat. **3.34** to yield **3.44** in 77% yield and 96% ee (Scheme 3.10).

**Scheme 3.10: Desymmetrization by ROM/CM**



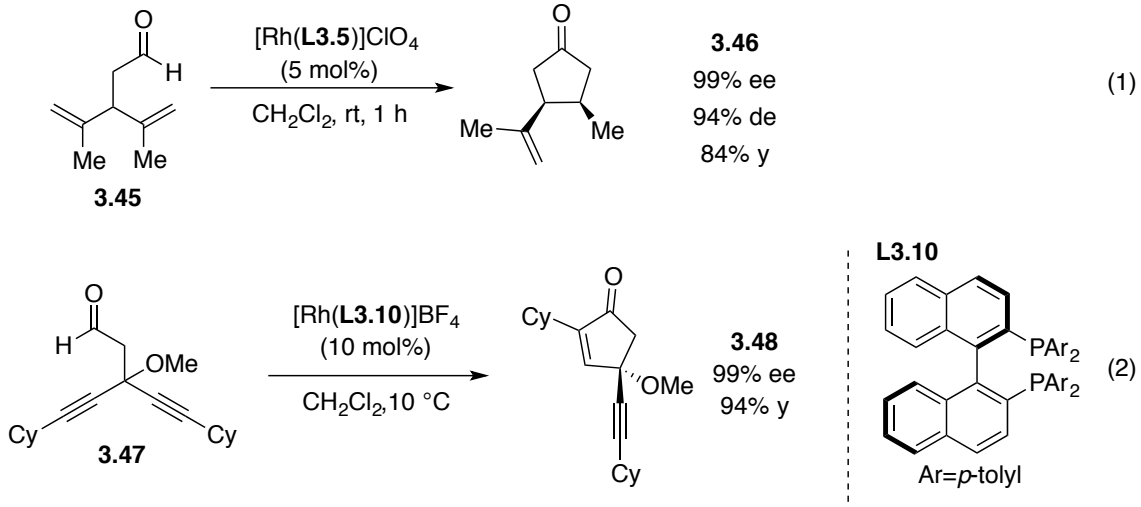

### *3.1.2.2 Desymmetrization of Dienes and Diynes via Hydroacylation*

Desymmetrization by hydroacylation is a very useful strategy as it can allow for concurrent formation of two stereocenters. In 1993, Sakai and co-workers developed an asymmetric Rh(I)-catalyzed hydroacylation of symmetric 3,4-disubstituted pentenals.[25] Reaction of aldehyde **3.45** with catalytic amounts of cationic rhodium-binap complex proceeded smoothly to afford cis-cyclopentenone (**3.46**) with high diastereo-and enantioselectivity (Scheme 3.11, eq. 1). The use of a cationic rhodium species was critical for high yields and enhanced rates compared to neural rhodium-ligand complexes. A few years later, Fu and co-workers were able to extend this strategy to the desymmetrization of diynes.[26] Using a similar cationic rhodium complex, diyne **3.47** is converted to **3.48** in 94% yield and 92% ee (Scheme 3.11, eq. 2). In non-coordinating solvents the methoxy

[25] (a) Wu, X.-M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1993**, *37*, 5927. (b) Tanaka, M.; Imai, M.; Fujio, M.; Sakamoto, E.; Takahashi, M.; Eto-Kato, Y.; Wu, X. M.; Funakoshi, K.; Sakai, K.; Suemune, H. *J. Org. Chem.* **2000**, *65*, 5806.
[26] Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10296.

group in **3.47** was necessary for an efficient desymmetrization, which is proposed to be due to coordination of the methoxy group to rhodium. The two-point coordination of the methoxy group and alkene leads to higher levels of organization leading to higher yields and enantioselectivities.

**Scheme 3.11: Asymmetric Intramolecular Hydroacylation by Sakai and Fu**




More recently, Dong and co-workers developed an asymmetric hydroacylation of bis(allyl)aldehydes to access cyclohexanones that contain $\alpha$-quaternary centers.[27] The use of a Rh-catalysts and biphep derivative **L3.11** mediates the intramolecular hydroacylation of **3.49** to yield cyclopentenone **3.50** with exceptional levels of yield and enantioselectivity (Scheme 3.12, eq. 1). The reaction is proposed to proceed *via* alkene isomerization followed by hydroacylation of the terminal olefin of intermediate **3.51**. Dong and co-workers have also presented the unique asymmetric intermolecular

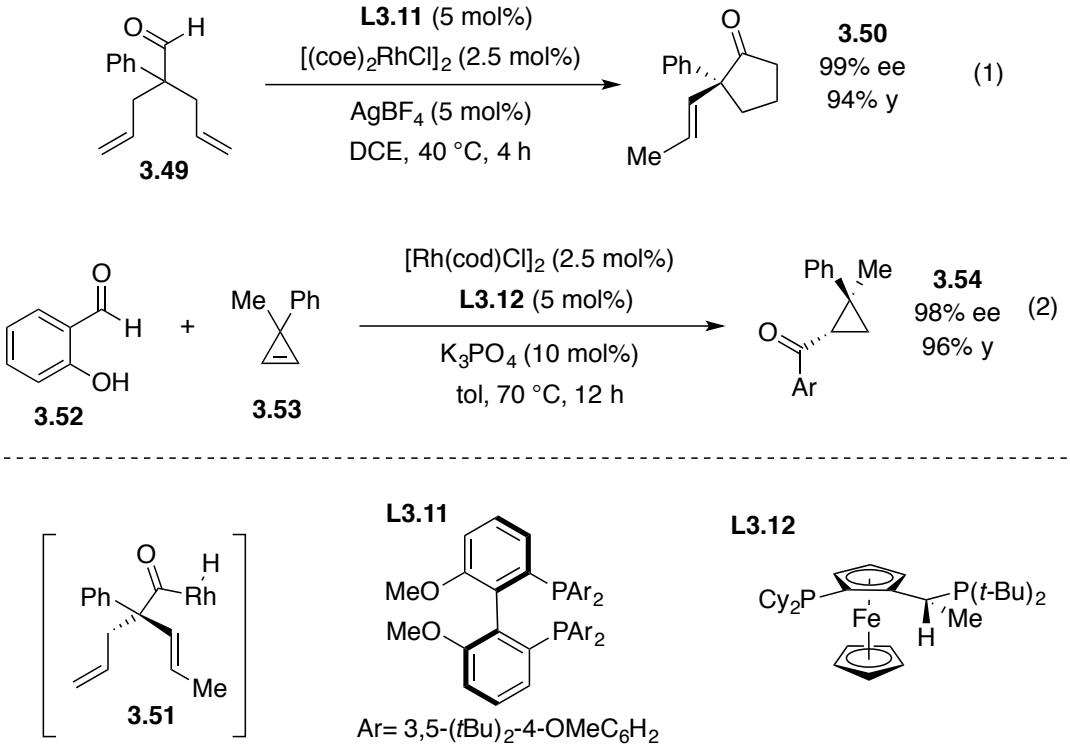
[27] Park, J.-W.; Kou, K. G. M.; Kim, D. K.; Dong, V. M. *Chem. Sci.* **2015**, *6*, 4479.

hydroacylation of cyclopropenes.[28] Rhodium-catalyzed hydroacylation of **3.53** with salicylaldehyde **3.52** in the presence of chiral Josiphos ligand **L3.12** yields cyclopropylketone **3.54** (Scheme 3.12, eq. 2). The salicylaldehyde is required because its phenolic oxygen is proposed to coordinate to rhodium, promoting the hydroacylation. Though the scope of the aldehyde is limited due to the need for coordination, this is a rare example of a highly enantioselective reaction of cyclopropene derivatives.[29]

[28] Phan, D. H. T.; Kou, K. G. M.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16354. For another example of asymmetric intramolecular hydroacylation see: Stemmler, R. T.; Bolm, C. *Adv*. *Synth. Catal*. **2007**, *349*, 1185.

[29] For other examples of asymmetric reactions of cyclopropenes see: (a) Sherrill, W. M.; Rubin, M. *J. Am. Chem. Soc.* **2008**, *130*, 13804. (b) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc*. **2000**, *122*, 978. (c) Liu, X.; Fox, J. M. *J. Am. Chem. Soc*. **2006**, *128*, 5600. (d) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198.

**Scheme 3.12: Rhodium-Catalyzed Asymmetric Desymmetrization by Hydroacylation by Dong and Co-Workers**



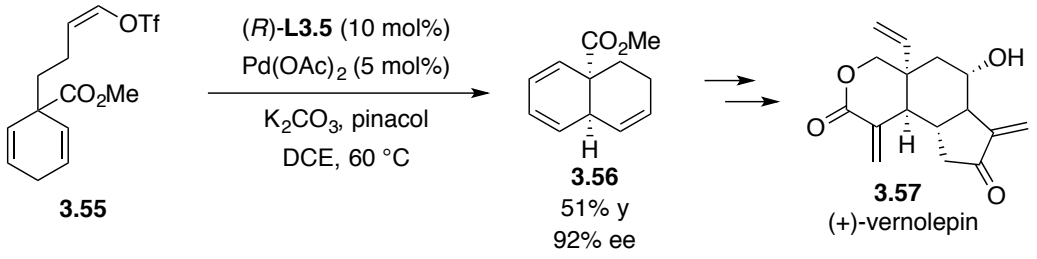

### *3.1.2.3 Desymmetrization by Heck Reactions*

Another well-developed strategy in the desymmetrization of symmetric alkenyl nucleophiles is through asymmetric palladium-catalyzed Heck reactions.[30] In efforts towards the synthesis of (+)-vernolepin **3.57**, Shibisaki and co-workers developed the first desymmetrization of symmetric dienes by a Heck reaction.[31] *cis*-Decalin **3.56** was obtained in 92% ee and 51% yield after palladium-cyclization of diene **3.55** in the presence

[30] For a review on asymmetric Heck reactions see: McCartney, D.; Guiry, P. J. *Chem. Soc. Rev.* **2011**, *40*, 5122.
[31] Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738.

of *(R)*-Binap **L3.5** at 60 °C (Scheme 3.13). Since this report, several efficient intramolecular desymmetrizing Heck reactions have been developed with dienes[32] and dienones.[33]

**Scheme 3.13: Desymmetrization of Prochiral Dienes by Shibisaki**




Application of the Heck reaction to the desymmetrization of cyclic alkenes has also been explored, and in recent years has been applied to the desymmetrization of substituted pentenes. In 2013, Zhou and co-workers developed a Pd-catalyzed desymmetrization of substituted cyclopentenes such as **3.50** via hydroarylation of aryltriflates with spirobiindane ligand **L3.13** (Scheme 3.14, eq. 1). The desymmetrization results in exclusive formation of the *trans*-cyclopentene **3.60**.[34] This asymmetric Heck reaction can also be applied to the hydroarylation of bicyclic alkenes such as norbornadiene with aryl triflates.

---

[32] (a) Sato, Y.; Sodeoka, M.; Shibaskai, M. *Chem. Lett.* **1990**, 1953. (b) Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589. (c) Ohari, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11737. (d) Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593. (f) Coperet, C.; Ma, S.; Negishi, E. *Angew. Chem. Int. Ed.* **1996**, *35*, 2125.

[33](a) Kondo, K.; Sodeka, M.; Mori, M.; Shibaskai, M. *Tetrahedron Lett.* **1993**, *34,* 4219. (b) Imbos, E.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184. For a review on asymmetric transformations of achiral dienones see: Katstahakken, K. A.; Harned, A. M. *Tetrahedron* **2014**, *70*, 9571.

[34] Liu, S.; Zhou, J. *Chem. Comm.* **2013**, *49*, 11758.

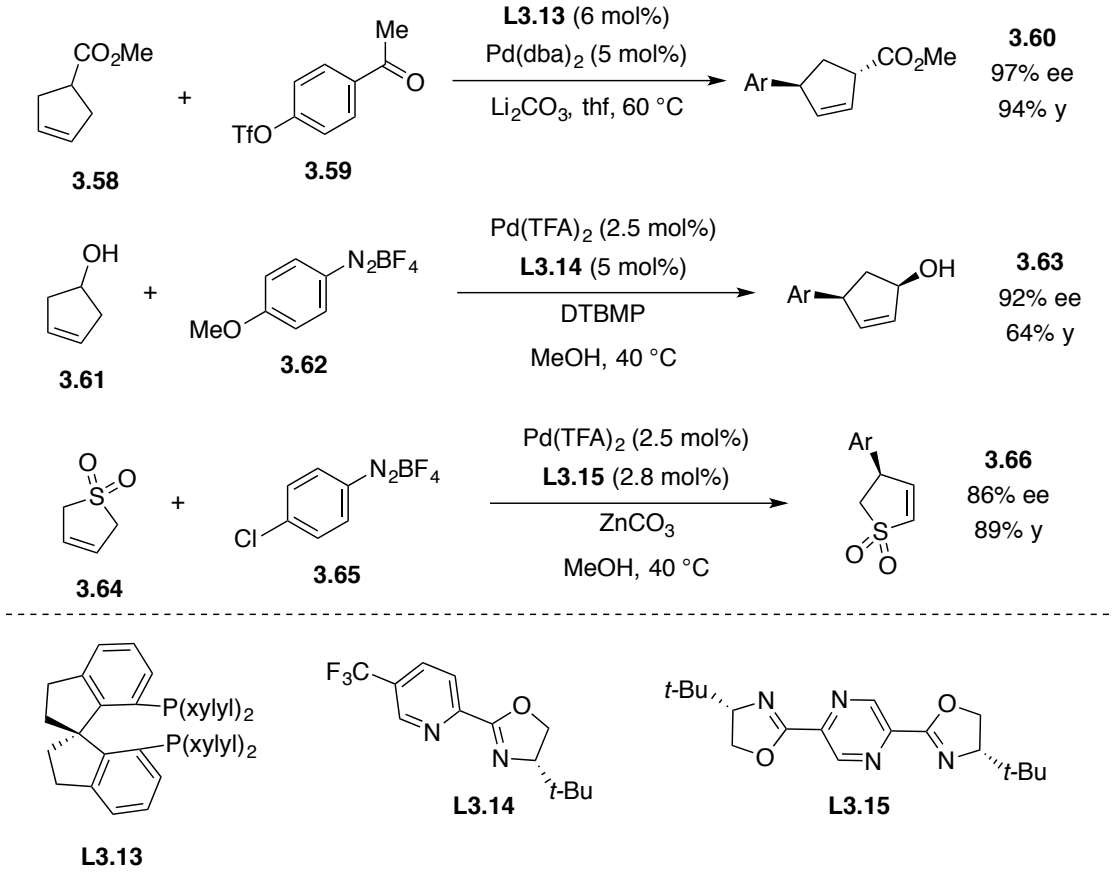
The use of aryldiazonium salts is popular in Heck reactions due to their rapid oxidative addition to palladium(0) to yield cationic palladium complexes. These electrophiles were first used by Matsuda and co-workers.[35] Correia and co-workers have had success in the application of these electrophiles in the desymmetrization of cyclic alkenes. Hydroarylation of hydroxypentene **3.61** in the presence of catalytic Pd(0) and PyOx ligand **L3.14** in a toluene methanol mixture yields desired **3.63** in high yield and enantioselectivity (Scheme 3.14, eq. 2).[36] Unlike the example by Zhou and co-workers, the free-hydroxyl group in **3.61** directs the catalyst to one $\pi$- face in the arylation resulting in the *cis* product. Correia and co-workers also developed a similar asymmetric Heck reaction of cyclic sulfoxides in presence of PyraBox ligand **L3.15** (Scheme 3.14, eq. 3).[37] This method can also be applied to the synthesis of S- and P-stereogenic cyclic olefins.

[35] Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, *6*, 159. For a review on the Matsuda-Heck reaction see: (a) McCartney, D.; Guiry, P. *J. Chem. Soc. Rev*. **2011**, *40*, 5122. (b) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, *2011,* 1403.

[36] De Oliveira Silva, J.; Angenes, R. A.; Menezes da Silva, V. H.; Servilha, B. M.; Adeel, M.; Braga, A. A. C.; Aponick, A.; Correia, C. R. D. *J. Org. Chem.* **2016**, *81*, 2010.

[37] de Azambuja, F.; Carmona, R. C.; Chorro, T. H. D.; Heerdt, G.; Correia, C. R. D. *Chem. Eur. J.* **2016**, *22*, 11205. For the first applications of PyraBox ligands see: Oliveria, C. C.; Pfaltz, A.; C. R. D. *Angew. Chem. Int. Ed.* **2015**, *54*, 14036.

**Scheme 3.14: Recent Asymmetric Heck Reactions of Cyclopentene Derivatives**




### *3.1.2.4 Desymmetrization by Suzuki Cross-Coupling*

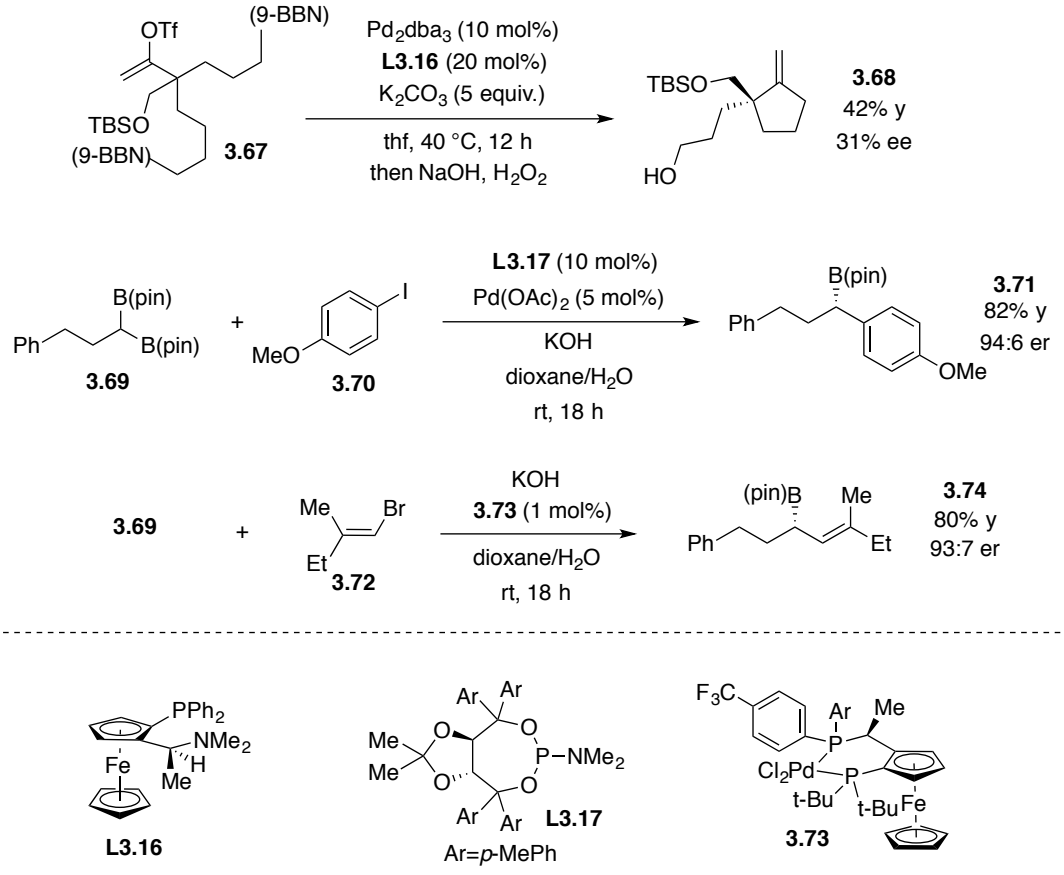
Though Suzuki cross-coupling reactions are prevalent in the literature, the desymmetrization of symmetric bis(boron) nucleophiles via cross-coupling are rare. The first example of this type of reaction was developed by Shibasaki and co-workers in 1998.[38] Bis(alkylborane) **3.67**, generated in situ by hydroboration, was converted to exocyclic pentene **3.68** *via* asymmetric palladium catalyzed cross-coupling (Scheme 3.15,

[38] Cho, S. Y.; Shibasaki, M. *Tetrahedron: Asymm*. **1998**, *9*, 3751

eq. 1). Though the asymmetric induction and yield of the reaction is poor, any level of enantioinduction in such a transformation is impressive. More recently, Morken and co-workers have demonstrated that symmetric geminal bis(boronate) **3.69** can undergo palladium-catalyzed asymmetric cross-coupling with aryl iodides in the presence of phosphoramidite ligand **L3.17** (Scheme 3.15, eq. 2).[39] Later, the asymmetric cross-coupling of geminal bis(boronates) was extended to include alkenyl halide electrophiles with the use of palladium-Josiphos complex **3.73** (Scheme 3.15, eq. 3).[40]

[39] Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534.
[40] Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 17918.

**Scheme 3.15: Desymmetrization of Symmetric Boron-Containing Electrophiles via Cross-Coupling**

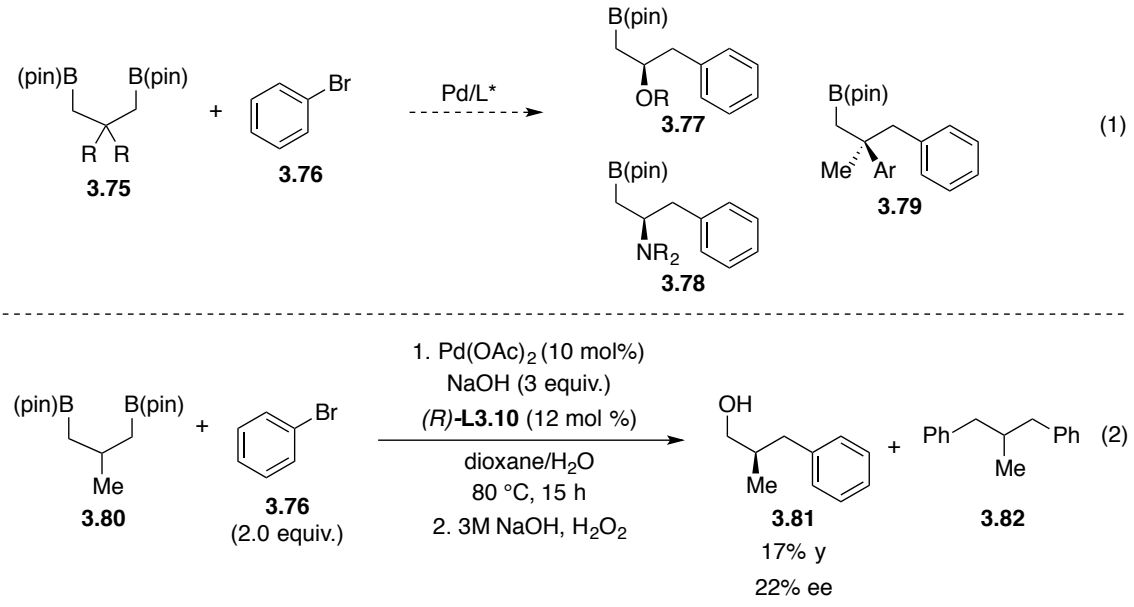



## 3.2 Desymmetrization of 1,3-Bis(Boronates) *via* Suzuki Cross-Coupling

In an effort to expand upon the desymmetrization of geminal bis(boronates) previously reported by our group (*vide supra*), we considered that a 1,3-bis(boronate) could participate in a similar desymmetrizing Suzuki coupling. The utility of this reaction could be broader than the desymmetrizations of geminal bis(boronates), which are limited to the synthesis of organoboron stereocenters. In the desymmetrization of 1,3-bis(boronates), the group at the prochiral center is unrelated to the position where cross-

coupling occurs, therefore a broad range of functionalized tertiary and quaternary stereocenters could be formed with the same fundamental reaction (Scheme 3.16, eq. 1). Previous Morken group member, Dr. Lichao Fang, worked on the development of this desymmetrization. After significant optimization, the best results for the Pd-catalyzed desymmetrization of **3.80** were obtained using (*R*)-**L3.10** (Scheme 3.11) with sodium hydroxide as a base at 80 °C in a $H_2O$/dioxane mixture (Scheme 3.16, eq. 2). Unfortunately, the desired product was only isolated in 17% yield and 22% ee; the rest of the mass balance consisted of recovered **3.80** and bis-coupled product **3.82**.

**Scheme 3.16: Desymmetrization of 1,3-Bis(Boronates) with Palladium**

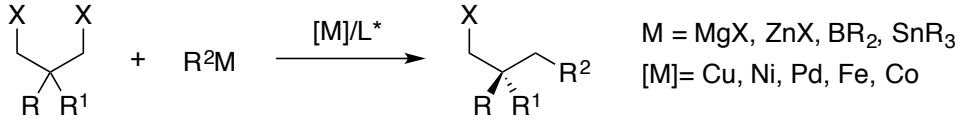



The low enantioselectivities could be due to high temperatures required for the reaction to proceed. The elevated temperatures needed are likely due to slow transmetalation of bis(boronate) **3.80** to the palladium center. The cross-coupling of alkyl

boronate nucleophiles is known to be difficult, often requiring alkoxide bases for activation.[41] This is not the case for the cross-coupling of geminal or vicinal bis(boronates), where cross-coupling can be performed at room temperature. In this case, transmetalation is facilitated by the adjacent boron, which can stabilize the Pd-alkyl complex after transmetalation, a feature which is not present in the cross-coupling of 1,3-bis(boronates).[42]

Though the desymmetrization of 1,3-bis(nucleophiles) failed to be effective we were still interested in developing a desymmetrization which would allow formation of diverse stereocenters. We predicted that this type of transformation could be accomplished *via* a metal -catalyzed cross-coupling of a symmetric bis(electrophile) (Scheme 3.17). Along these lines, alkyl halides and pseudo halides have been shown to engage in efficient cross-couplings with a variety of transition metal catalysts under mild conditions and we envisioned they could be useful here.

**Scheme 3.17: Proposed Desymmetrization of Prochiral Bis(electrophiles)**




[41] For examples of unactivated alkyl boronates in cross-coupling reactions see: (a) Yang, C-T.; Zhang, Z-Q.; Tajuddin, H.; Wu, C-C.; Liang, J.; Liu, J-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem. Int. Ed*. **2012**, 51, 528. (b) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405. (c) Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761. (d) Zou, G.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817.

[42] (a) Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033. (b) Endo, K.; Ohkubo, T.; Shibata, T. *Org. Lett*. **2011**, *13*, 3368. (c) Endo, K.; Ohkubo, T.; Ishioka, T.; Shibata, T. *J. Org. Chem*. **2012**, 77, 4826.

## 3.3 Metal Catalyzed Cross-Coupling of Unactivated Alkyl Electrophiles

### *3.3.1 Introduction to Cross-Coupling of Alkyl Electrophiles*

Transition-metal catalysts have found broad use in $sp^2$-$sp^2$, $sp^2$-sp, and sp-sp cross-coupling reactions. The application of transition-metal catalysts in cross-couplings of $sp^3$ electrophiles is less developed, but these types of reactions can be used to form important C-C bonds.[43] Recent studies have shown that building complexity by the addition of $sp^3$ carbons in drug candidates leads to molecules with less off-target effects, higher solubility and a higher degree of success in clinical trials.[44] Discovery of efficient metal-catalyzed cross-coupling reactions of $sp^3$ electrophiles will aid in the synthesis of molecules with high degrees of saturation. Several current strategies in the cross-coupling of alkyl electrophiles require the presence of an adjacent activating group, such as a $sp^2$ or sp carbon.[45] Though examples of unactivated alkyl electrophiles in the literature are

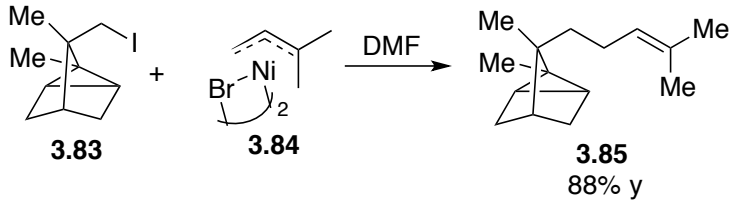
[43] For a review on transition metal catalyzed activation of C-X bonds in cross-coupling reactions see: Luh, T.-Y.; Leung, M.; Wong, K. T. *Chem. Rev.* **2000**, *100,* 3187.
[44] (a) Lovering, F.; Bikker, J.; Humbelt, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Dandapani, S.; Marcaurelle, L. A. *Nat. Chem. Bio.* **2010**, *6*, 861. (c) Mendez-Lucio, O.; Mendina-Franco, J. L. *Drug Discov. Today* **2017**, *22*, 120. (d) Stotani, S.; Lorenz, C.; Winkler, M.; Medda, F.; Picazo, E.; Martinex, O.; Karawajczky, A.; Sanchez-Quesada, J.; Giordanello, F. *ACS Comb. Sci.* **2016**, *18*, 330. (e) Firth, N. C.; Brown. N.; Blagg, J. *J. Chem. Info. Mod.* **2012**, *52*, 2516.
[45] For a review on cross-coupling of activated alkyl electrophiles see: (a) Tollefson, E. J.; Hanna, L. E.; Jarvo, E. R. *Acc. Chem. Res.* **2015**, *48*, 2344. (b) Glorius, F. *Angew. Chem. Int. Ed.* **2008**, *47*, 8347.

limited, several different transition-metals have been shown to catalyze these reactions including: Ni, Pd, Cu, Co, and Fe.[46]

### *3.3.2 Cross-Coupling of Unactivated Alkyl Electrophiles with Nickel*

In 1967, the first example of a transition-metal mediated cross-coupling of an unactivated alkyl halide was presented by E. J. Corey.[47] Though the exact mechanism was not known, iodide **3.83** was efficiently transformed to **3.85** in the presence of stoichiometric $\pi$-allylNi(I) bromide **3.84** (Scheme 3.18). This cross-coupling was also selective for the coupling of an alkyl iodide in the presence of an alkyl chloride.

**Scheme 3.18: Seminal Example of Transition-Metal Cross-Coupling of Unactivated Alkyl Halides**




**3.83** **3.84** **3.85**
88% y

It would be over 20 years before a catalytic nickel-catalyzed Kumada-Corriu coupling of alkyl iodides was developed by Scott and co-workers.[48] Ni(dppf)$Cl_2$ was used

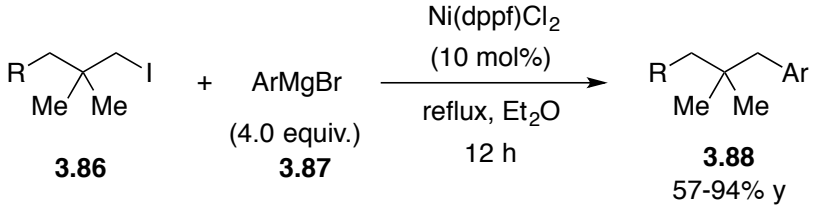
[46] For examples of Co-catalyzed cross-couplings of unactivated alkyl electrophiles see: Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. *Synlett,* **2009**, *2009*, 2931. For selected examples of Fe-catalyzed cross-couplings of unactivated alkyl electrophiles see: (a) Tamura, M.; Kochi, J. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Fürstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) Fürstner, A.; Martin, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955 (d) Dongol, K. G.; Koh, H.; Sau, M.; Chai, C. L. L. *Adv. Synth. Catal.* **2007**, *349*, 1015.

[47] Corey, E. J.; Semmelhack, M. F. *J. Am. Chem. Soc.* **1967**, *89*, 2755.

[48] Yuan, K.; Scott, W. J. *Tetrahedron Lett.* **1990**, *32,* 189.

to catalyze the cross-coupling of aromatic Grignard reagents with unactivated neopentyl iodides **3.86** (Scheme 3.19). The reaction was, however, limited to neopentyl iodides, as homocoupling of the electrophile was noted as a problem with non-hindered electrophiles.

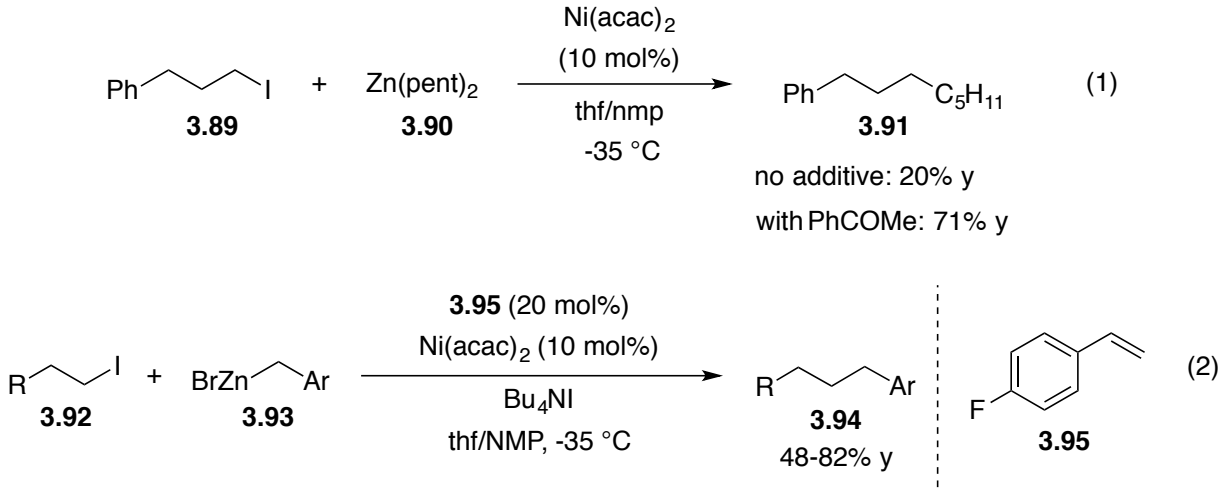
**Scheme 3.19: Kumada-Corriu Cross-Coupling of Alkyl Iodides by Scott and Co-Workers**




Knochel and co-workers have demonstrated, on several occasions, that the nickel-catalyzed Negishi cross-coupling of simple alkyl electrophiles can be facilitated by the addition of electron deficient olefins (Scheme 3.20, eq. 1).[49] In initial studies, acetophenone was used as a stoichiometric additive but in later studies styrene derivative **3.95** was found to be a superior additive (Scheme 3.20, eq. 2).[50] The olefin additives are believed to promote reductive elimination by the removal of electron density from the metal center.

[49] Giovannini, R.; Studenmann, T.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 2387.
[50] Jensen, A.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79.

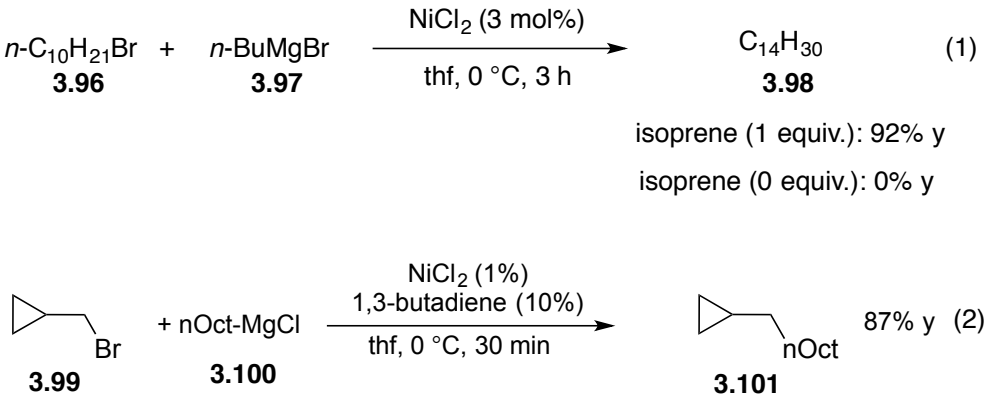
**Scheme 3.20: Effect of Electron Deficient Additives to Nickel-Catalyzed Cross-Coupling Reactions**




Kambe and co-workers also used this strategy in their nickel-catalyzed Kumada coupling with alkyl halides and pseudohalides.[51] In this case, diene additives were discovered to be highly effective for the cross-coupling of alkyl halides with 92% yield of **3.98** obtained in the presence of isoprene, but only 2% yield in the absence of the additive (Scheme 3.21, eq. 1). The mechanism of the reaction is proposed not to include radical intermediates as cyclopropyl bromide **3.99** does not ring-open under the reaction conditions (Scheme 3.21, eq. 2) The remarkable effect the dienes have on reactivity is rationalized by a unique oxidative cyclization of the diene to give a different diene (*vide infra*). The same group has also applied diene additives in copper-catalyzed Kumada cross-couplings of alkyl iodides.[52]

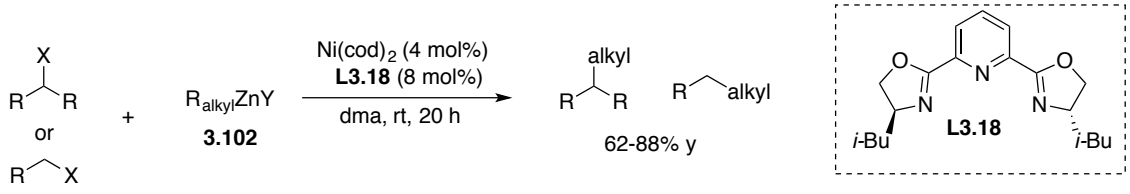
[51] Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222.
[52] Shen, R.; Iwasaki, T.; Terao, J.; Kambe, N. *Chem. Comm.* **2012**, *48*, 9313.

**Scheme 3.21: Cross-Coupling of Alkyl Halides in the Presence of Diene Additives by Kambe**




Though most examples of alkyl halides in cross-coupling reactions are limited to primary electrophiles, Greg Fu and co-workers have developed a Negishi cross-coupling that can be applied to secondary and primary alkyl bromides and iodides.[53] An array alkyl halides participate readily in cross-coupling with alkyl zinc bromides in the presence of PyBox ligand **L3.18** and $Ni(cod)_2$ catalyst (Scheme 3.22).

**Scheme 3.22: Negishi Cross-Coupling of Secondary Alkyl Electrophiles by Fu**




In addition to Kumada and Negishi coupling reactions, nickel has been used as a catalyst in Suzuki couplings of unactivated alkyl electrophiles.[54] In 2004, Greg Fu and co-

[53] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726.

[54] For other examples of Ni-catalyzed Suzuki cross-couplings of unactivated alkyl electrophiles see: (a) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340. (b) Gonzalez-

workers found that catalytic $Ni(cod)_2$ with bathophenanthroline ligand **L3.19** was effective for the cross-coupling of secondary or primary alkyl halides with unsaturated boronic acids (Scheme 3.23, eq. 1).[55] A few years later the same group developed a stereoconvergent cross-coupling of secondary alkyl halides **3.104** with alkyl-(9-BBN) nucleophiles **3.105** using a chiral diamine ligand **L3.20** (Scheme 3.23, eq. 2).[56] The high levels of enantioinduction in this type of reaction are impressive, but the scope is limited. The β-aryl group on the electrophile is necessary for high enantioselectivities. The cross-coupling of alkyl-(9-BBN) nucleophiles has also been accomplished using an amidobis(amine) pincer complex **3.109** by Xile Hu and co-workers (Scheme 3.23, eq. 3).[57] The mechanism of this cross-coupling was determined to occur through radical activation of alkyl halides. Though there are several examples of Suzuki coupling reactions of alkyl electrophiles with nickel-catalysts, palladium has primarily been used as a catalyst for these coupling partners.

---

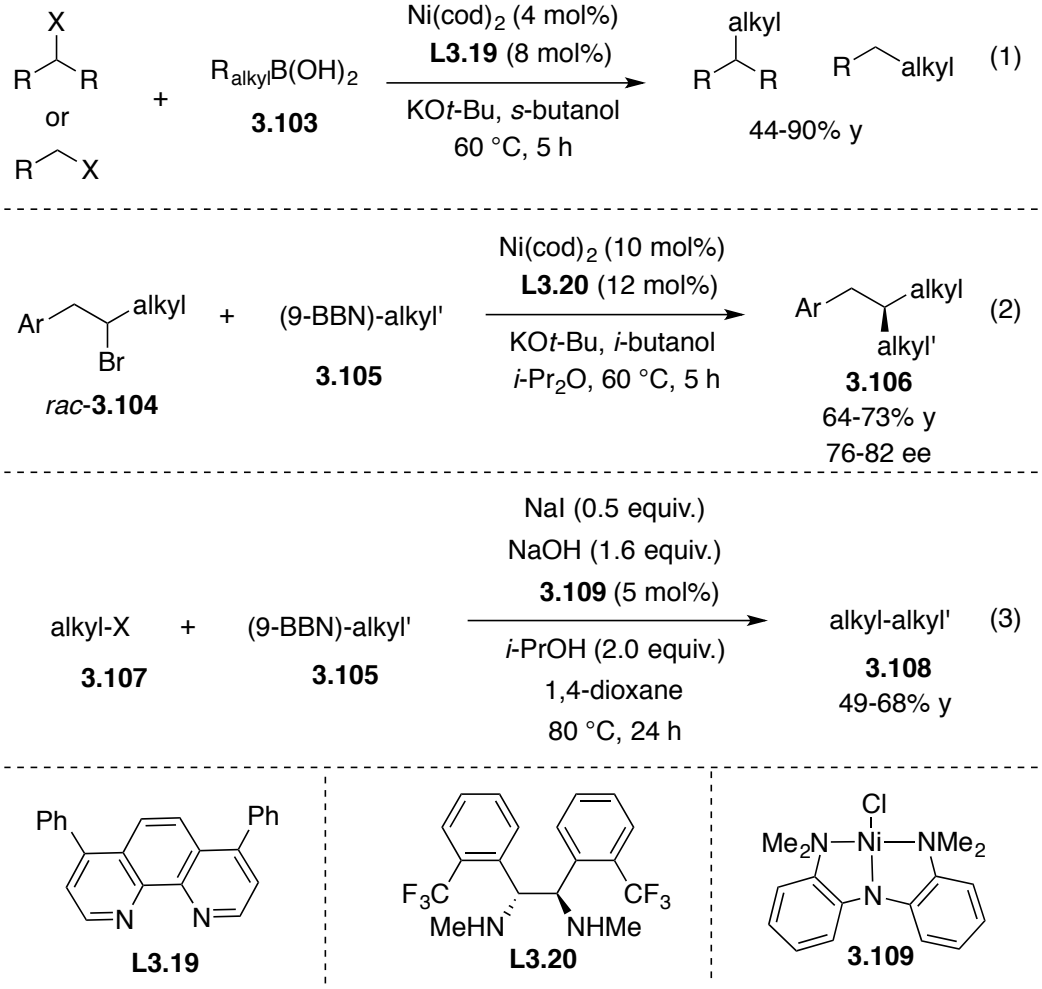
Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360. (c) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129,* 9602. (d) Lu, Z.; Fu, G. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6676.

[55] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340.

[56] Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130,* 6694.

[57] Di Franco, T.; Boutin, N.; Hu, X. *Synthesis* **2013**, *45*, 2949.

**Scheme 3.23: Ni-Catalyzed Suzuki Cross-Coupling of Alkyl Electrophiles**



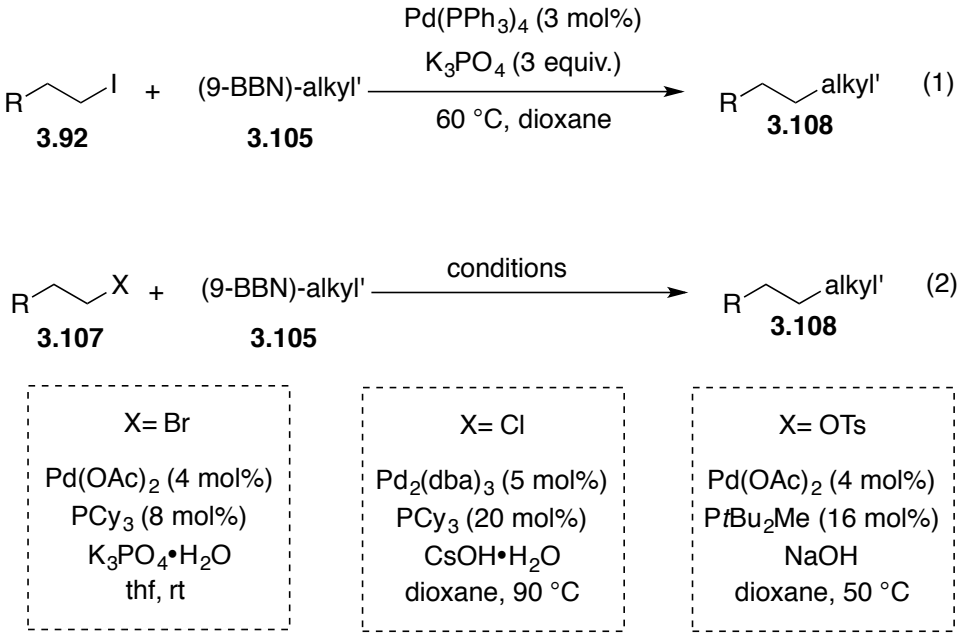

### *3.3.3 Cross-Coupling of Unactivated Alkyl Electrophiles with Palladium*

Suzuki and co-workers presented the first examples of palladium-catalyzed cross-coupling of unactivated alkyl electrophiles. The cross-couplings of alkyl iodides with alkyl-(9-BBN) nucleophiles was accomplished using a $Pd(PPh_3)_4$ catalyst (Scheme 3.24, eq. 1).[58] Oxidative addition of the alkyl halide in this case is also proposed to proceed via a radical

[58] Ishiyama, T.; Abe, N.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 21, 691.

process. Fu and co-workers were later able to extend this method to include alkyl bromides, alkyl tosylates and alkyl chlorides (Scheme 3.24, eq. 2).[59] The reaction is extremely sensitive to the structure of the phosphine ligand.[60] For example the cross-coupling of alkyl bromides with $PCy_3$ proceeds smoothly to give cross-coupled product while P(*i*-Pr)$_3$ gives no desired product under the same conditions.[61] Fu and co-workers have applied similar conditions to accomplish a Negishi cross-coupling of alkyl halides and pseudohalides.[62]

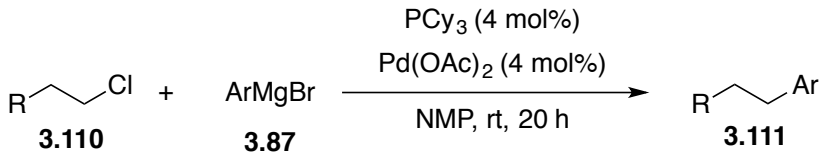
**Scheme 3.24: Palladium-Catalyzed Suzuki Cross-Coupling of Alkyl Electrophiles**




[59] (a) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1945. (b) Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910.
[60] Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003,** *42*, 5749. Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *124*, 13662.
[61] Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.
[62] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527.

Beller and co-workers developed an efficient palladium-catalyzed Kumada coupling of alkyl chlorides with $PCy_3$ as a ligand (Scheme 3.25).[63] Unlike the Suzuki cross-coupling developed by Fu and co-workers, the Kumada coupling of alkyl chlorides was not highly sensitive to ligand structure as $PtBu_3$ also gave significant yields of product. In fact, a year later N-heterocyclic carbene ligands were found to be suitable for the same transformation.[64]

**Scheme 3.25: Pd-Catalyzed Kumada Coupling of Alkyl Electrophiles by Beller**




Though, palladium catalysts have found use as catalysts in cross-coupling reactions of alkyl halides, the past several years have seen more use of copper, nickel and iron catalysts in these types of transformations. This is likely due to lower propensity for β-hydride elimination in catalytic intermediates and lower cost of metal precatalysts.

[63] Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed*. **2002**, *41*, 4056.
[64] Frisch, A. C.; Rataboul, F.; Zapf, A.; M. Beller, M. *J. Organomet. Chem*. **2003**, *687*, 403.

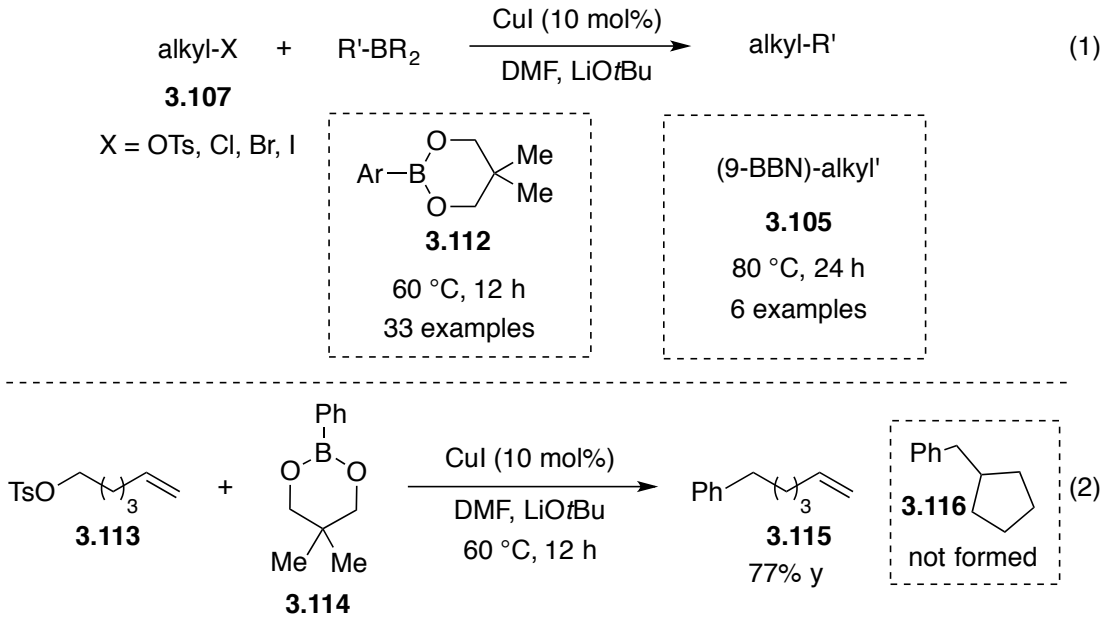
### *3.3.4 Cross-Coupling of Unactivated Alkyl Electrophiles with Copper*

Copper has seen significant use as a catalyst for the cross-coupling of alkyl electrophiles[65] and in recent years has even been applied in difficult $sp^3$-$sp^3$ cross-couplings of hindered systems. In 2011, Liu and co-workers developed a Cu-catalyzed Suzuki-Miyaura coupling of alkyl halides and pseudohalides. Both aryl boronate esters **3.112** and alkyl-(9-BBN) nucleophiles efficiently cross-couple to an array of alkyl electrophiles with a CuI catalyst in DMF at 80 °C with Li*t*-OBu as the base (Scheme 3.26, eq. 1).[66] In order to understand the mechanism of the reaction, tosylate **3.113** was used in the reaction and **3.115** was obtained as the exclusive product (Scheme 3.26, eq. 2). This result suggests that the reaction does not operate by a radical mechanism, if this were the case then cyclopentyl **3.116** would likely form during cross-coupling by radical cyclization.

[65] For reviews on Cu-catalyzed cross-coupling reactions see: (a) Erdik, E. *Tetrahedron*, **1984**, *40*, 641. (b) Cardenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Evano, G.; Theunissen, C.; Pradal, A. *Nat. Prod. Rep.* **2013**, *30*, 1467.

[66] Yang, C.-T.; Zhang, Z. Q.; Liu, Y.-C.; Liu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 3904.

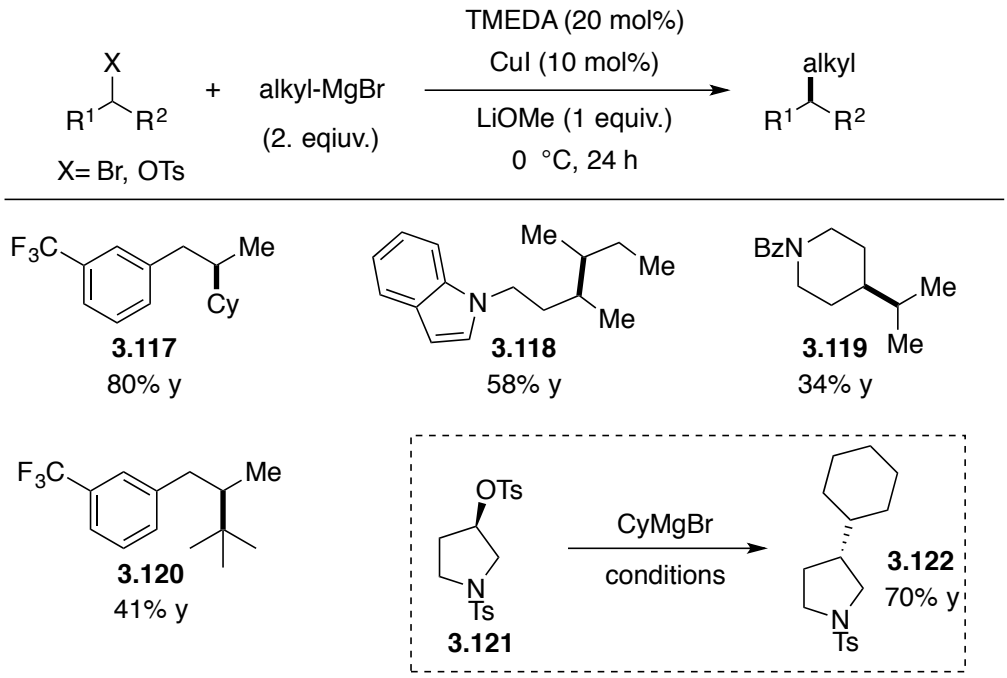
**Scheme 3.26: Cu-Catalyzed Suzuki-Miyaura Coupling By Liu**




A year later, the Liu group developed a Cu-catalyzed Kumada coupling with a significantly expanded scope using TMEDA as a ligand.[67] This cross-coupling can be performed to build very hindered C-C bonds from tertiary nucleophiles and secondary electrophiles at low temperatures (Table 3.1). This reaction was also demonstrated to proceed in the absence of radical species. Subjection of enantioenriched tosylate **3.121** to cross-coupling with cyclohexylmagnesium bromide produces **3.122** in 70% yield with inversion of configuration (Table 3.1). This result supports the hypothesis that the copper-catalyzed Kumada coupling proceeds by an $S_N2$ mechanism.

[67] Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, *134*, 11124.

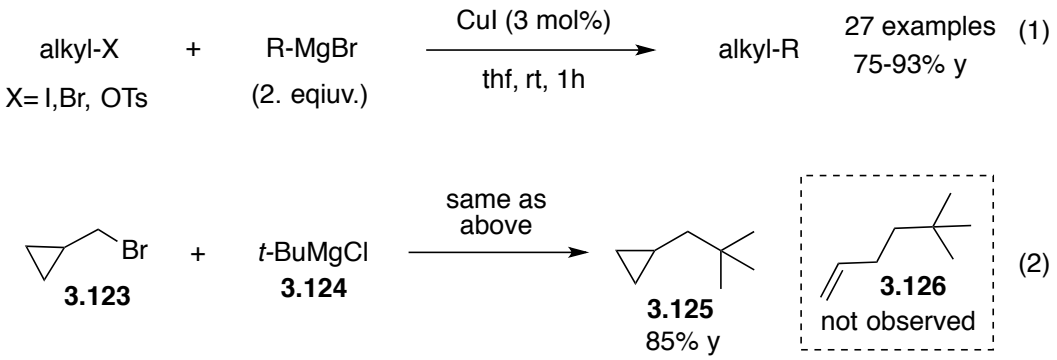
**Table 3.1: Cu-Catalyzed Kumada Coupling By Liu**




In the same year, a similar copper-catalyzed Kumada coupling of primary alkyl electrophiles was reported by Hu and co-workers.[68] In the absence of ligand, CuI catalyzes the cross-coupling of alkyl tosylates and halides with hindered nucleophiles at room temperature (Scheme 3.27, eq. 1). Performing the cross-coupling on an electrophile containing a radical clock yielded no products derived from radical intermediates and only direct cross-coupling product **3.125** (Scheme 3.27, eq. 2). In accord with previous reports on Cu-catalyzed cross-coupling reactions of alkyl halides, this reaction is proposed to proceed via an $S_N2$ mechanism.

[68] Ren, P.; Stern, L.-A.; Hu, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 9110.

**Scheme 3.27: Kumada Coupling of Alkyl Electrophiles with Copper by Hu**



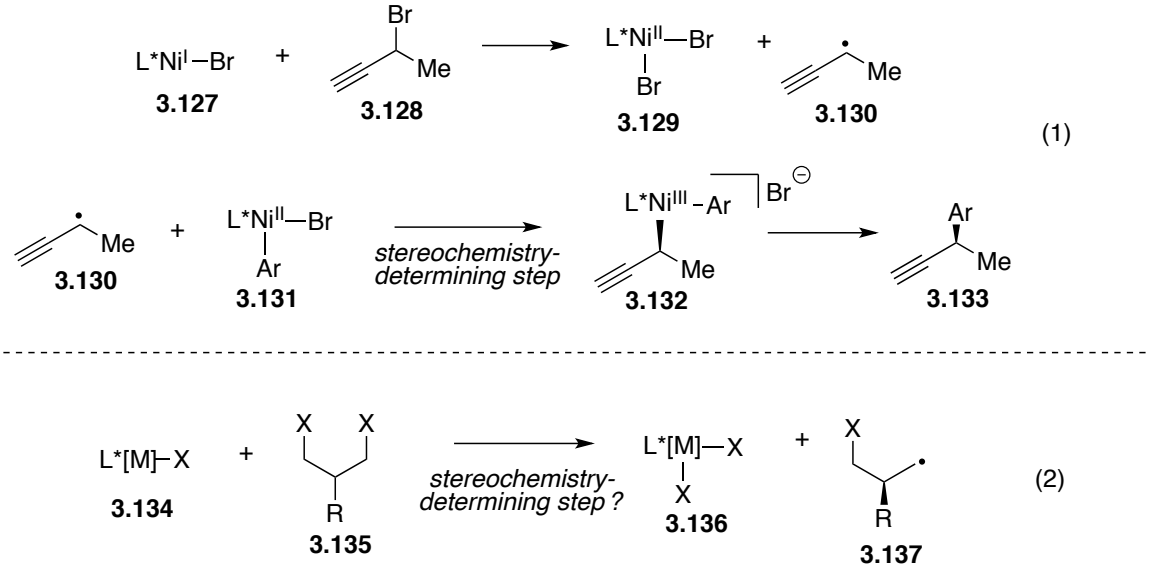

Due to the significant number of previously developed transition-metal catalyzed cross-coupling reactions which efficiently engage alkyl halides and pseudohalides, we believed that with the correct choice of electrophile, metal, ligand and conditions an efficient desymmetrization of 1,3-biselectrophiles could be developed.

## 3.4 Desymmetrization of Symmetric Bis(electrophiles)

We predicted that the choice of electrophile would be extremely important in allowing for a highly selective asymmetric cross-coupling reaction. Though a majority of the previous examples of C-$sp^3$ metal-catalyzed cross-coupling reactions utilize alkyl halides as electrophiles, we envisioned that meso-1,3-bishalides would be non-ideal for a desymmetrization. Alkyl halides have previously been proposed to participate in Pd- and Ni-catalyzed cross-coupling reactions *via* single electron oxidative additions (*vide supra*). In a 2014 study of the mechanism of a Ni-catalyzed stereoconvergent Negishi arylation of propargylic bromides, Fu and Schely determined that the reaction proceeds by a radical

chain reaction (Scheme 3.28, eq. 1).[69] A nickel(I)bromide formed in situ abstracts a halogen from the propargyl electrophiles resulting in propargylic radical species **3.130**. Recombination of **3.130** with L*Ni(II)ArBr **3.131** followed by reductive elimination yields the product; when a chiral ligand is employed the recombination is stereodefining. If the proposed desymmetrization were to proceed by this mechanism, halogen activation by an outer-sphere electron transfer would need to be stereodefining (Scheme 3.28, eq. 2). However, due to a lack of substrate-catalyst interaction during an outer-sphere electron transfer, we suspected it would be difficult for a chiral ligand on metal to control the stereochemical outcome.

**Scheme 3.28: Use of *meso*-1,3-Bishalides in Desymmetrization**

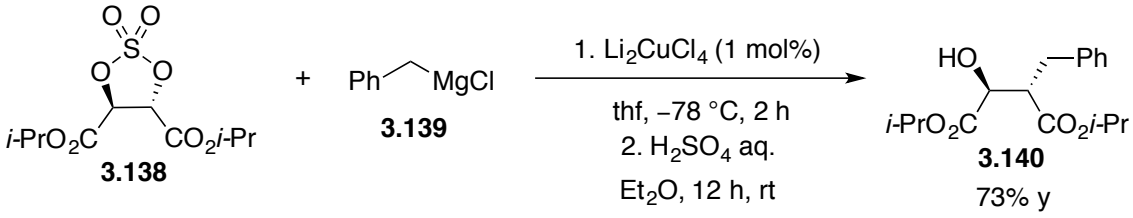



[69] Schley, N.; Fu, G. *J. Am. Chem. Soc.* **2014**, *136,* 16588

We expected that a highly enantioselective cross-coupling of a prochiral bis(electrophile) would be most likely to result from a controlled $S_N2$-type oxidative addition with a chiral-metal species. In addition to the stereochemical concerns when employing alkyl halides, it was suspected that with halides bis(coupling) to each of the halides would likely be an issue, similar to what was observed with the 1,3-bis(boronate) desymmetrization (*vide supra*). We expected that other electrophiles might circumvent this issue.

Transition-metal catalyzed cross-coupling reactions that can be applied to alkyl pseudohalides such as mesylates and tosylates, have been proposed to proceed via $S_N2$ type mechanisms (*vide supra*).[70] In addition to the examples previously described involving mesylates and tosylates, Sharpless and co-workers demonstrated that cyclic sulfate **3.138** can engage in cross-coupling with benzyl magnesium chloride in the presence of a copper catalyst via and invertive $S_N2$ type oxidative addition (Scheme 3.29).[71]

**Scheme 3.29: First Example of Cross-Coupling with Cyclic Sulfate Electrophiles**

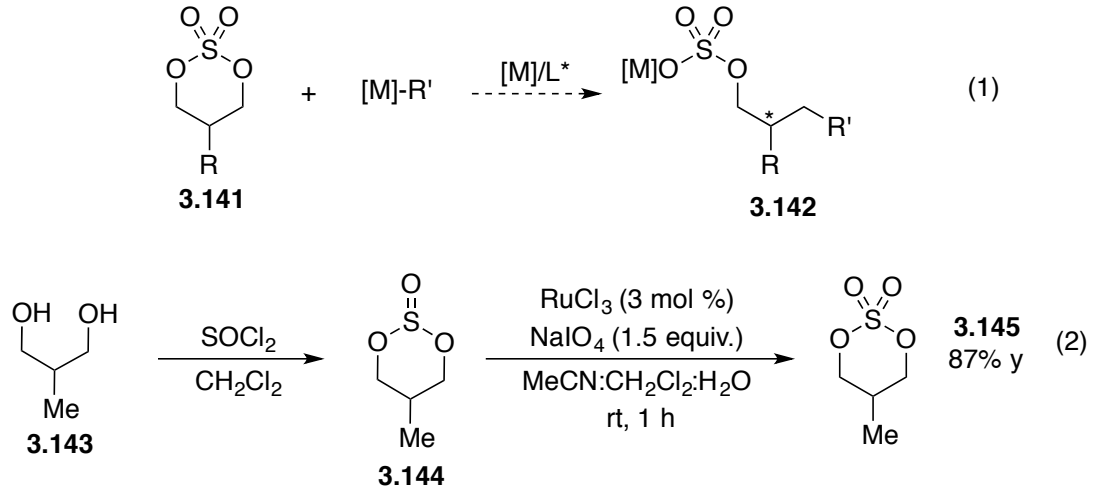



[70] Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222.
[71] Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.

Though cyclic sulfates have seen limited use as electrophiles in cross-coupling reactions,[72] these substrates have several important features which we believed would make them ideal electrophiles for the proposed desymmetrization reaction (Scheme 3.30, eq. 1). First and foremost, two-electron redox processes should be favored with these electrophiles, avoiding any type of predictably nonselective outer-sphere single electron activation. In addition, cyclic sulfates should not be prone to bis(coupling), due to the attenuated reactivity of the remaining C-O bond after initial coupling. The cyclic nature of the prochiral sulfate will also help by likely limiting the number of conformational isomers available to participate in the cross-coupling reaction compared to an acyclic bis(electrophile). In addition, cyclic sulfates such as **3.145** are also readily available in two steps from commercially available diols (Scheme 3.30, eq. 2).

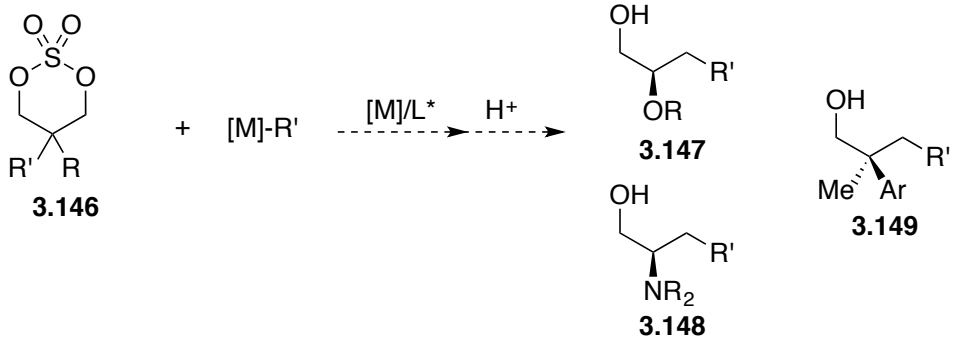
[72] For other example of cyclic sulfates as electrophiles in cross-coupling reactions see: (a) Byun, H.-S.; Sadlofsky, J. A.; Bittman, R. *J. Org. Chem.* **1998**, *63*, 2560. (b) Ramirez-Contreras, R.; Morandi, B. *Org. Lett.* **2016**, *18*, 3718. (c) Gilles, A.; Martinez, J.; Cavelier, F. *J. Org. Chem.* **2009**, *74*, 4298. For related cyclic sulfamidates as electrophiles see: (a) Ursinyova, N.; Bedford, R. B.; Gallagher, T. *Eur. J. Org. Chem.* **2016**, *2016*, 673. (b) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748. (c) When, P. M. Du Bois, J. *Org. Lett.* **2005**, *7*, 4685.

**Scheme 3.30: Synthesis and Proposed Desymmetrization of Cyclic Sulfates**




Unlike a stereoconvergent cross-coupling where the reaction occurs at the forming stereocenter, the desymmetrization of cyclic sulfates via cross-coupling would likely not be effected by different groups at the prochiral center. Thus, this method would allow the synthesis of a diverse range of products through one method (Scheme 3.31). With cyclic sulfate **3.145** in hand, we began the development of a metal-catalyzed asymmetric cross-coupling which could efficiently desymmetrize these biselectrophiles.

**Scheme 3.31: Utiltiy of Desymmetrization of Cyclic sulfates**

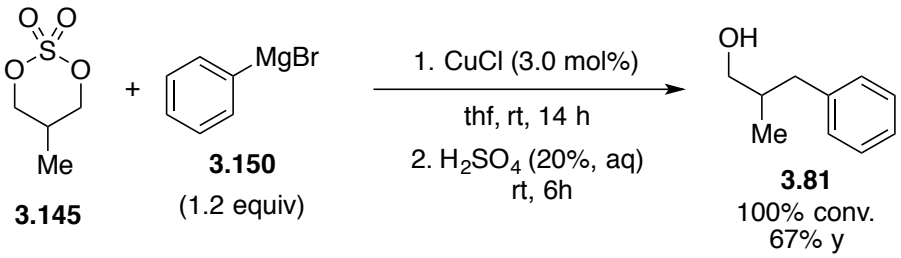


## 3.5 Development of the Desymmetrization of Cyclic Sulfates [73]

### *3.5.1 Development of the Desymmetrization with Copper Catalysts*

Our initial efforts to develop an efficient desymmetrization of cyclic sulfates focused on the development of an asymmetric copper-catalyzed cross-coupling. Copper was initially investigated because it is the only metal that has previously been used in cross-couplings of cyclic sulfates (*vide supra*). Using conditions similar to those developed by Beller and co-workers in the Cu-catalyzed Kumada coupling of alkyl halides and pseudo halides, we were pleased to see that cyclic sulfate engaged in cross-coupling with PhMgBr in the presence of catalytic CuCl (Scheme 3.32).

**Scheme 3.32: Initial Results in Kumada Coupling of Cyclic Sulfate 3.145 with Copper**



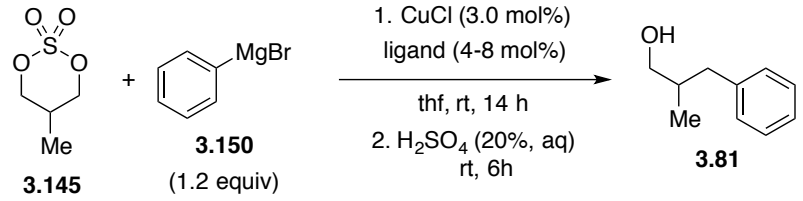

It is important to note that the PhMgBr was chosen over allylMgX and benzylMgX, which have previously been used in cross-coupling reactions with cyclic sulfates, because these nucleophiles were determined to add to cyclic sulfates without a catalyst.[74] Since

[73] Eno, M. S.; Lu, A.; Morken, J. P. *J. Am. Chem. Soc.* **2016**, *138,* 7824.
[74] Ramirez-Contreras, R.; Morandi, B. *Org. Lett.* **2016**, *18*, 3718.

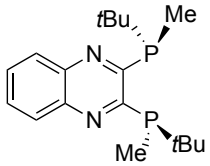
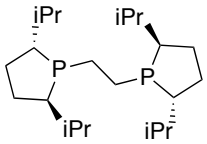
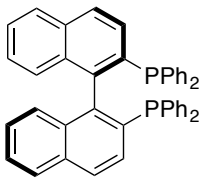
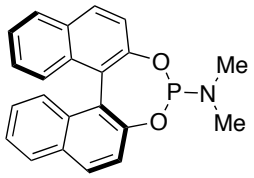
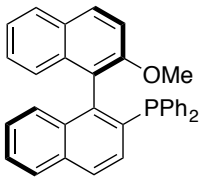
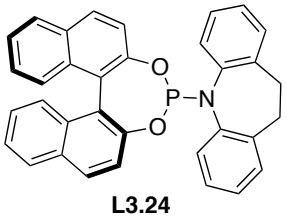
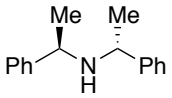
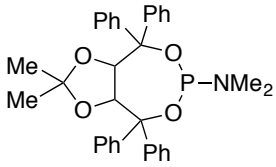
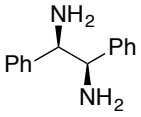
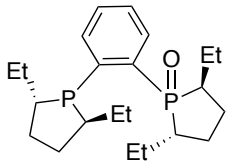
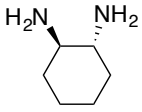
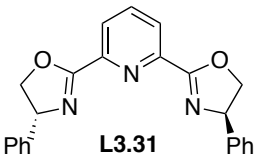
we determined that there is no formation of desired product without catalyst when using PhMgBr, we began to examine chiral ligands in this system. Unfortunately, after investigating an array of chiral ligand scaffolds none gave appreciable levels of enantioinduction (Table 3.2). [75]

[75] Though several ligand scaffolds were tested, NHC ligands were never examined reaction. NHC ligand are popular in asymmetric copper-catalyzed reactions due their strong sigma donating ability and modular synthesis, for review on the use of NHC ligands in asymmetric reactions see: Wang, F.; Liu, L.-J.; Wang, W.; Li, S.; Shi, M. *Coord. Chem. Rev.* **2012**, *256*, 804.

**Table 3.2: Investigation of Chiral Ligands In Cu-Catalyzed Kumada Coupling**




**3.145** **3.150** (1.2 equiv) **3.81**

| | | | |
|---|---|---|---|
|  **L3.21** 23% y 0% ee |  **L3.22** 44% y 0% ee |  **L3.5** 36% y 0% ee |  **L3.23** 46% y 1.5% ee |
|  **L3.7** 46% y 1% ee |  **L3.24** 46% y 2% ee |  **L3.25** 13% y 0% ee |  (*R,R*)-**L3.26***:* 2% ee, 60% y (*S,S*)-**L3.26***:* -1.5% ee, 62% y |
|  **L3.28** 23% y 0% ee |  **L3.29** 66% y 0% ee |  **L3.30** 27% y 0% ee |  **L3.31** 46% y 0% ee |

[a] Reactions employed 0.3 mmol of **3.145**. [b] yield of purified product. [c] enantiomer ratios were determined by SFC analysis on chiral stationary phase.

In terms of reactivity, the best results were obtained with TADDOL-derived phosphoramidite ligand **L3.26**, where 2% ee of product was obtained with the (*R,R*)-**L3.26** and -1.5% ee obtained with (*S,S*)-**L3.26**. The opposing ratios indicate that the level of enantioinduction is real and not an error in analysis. Attempts to enhance the

enantioselectivity of the reaction with **L3.26** by slow addition of Grignard reagent, changing solvent, temperature, and Cu-precatalyst did not lead to an improved reaction. In addition, the use of zinc and boron based nucleophiles in the copper catalyzed cross-coupling of **3.145** did not yield any product. The lack of asymmetric coupling with copper could be due poor copper-ligand complexation and oxidative addition occurs with a ligand-free copper species. Since a ligand scaffold able to give high enantioselectivities in the copper-catalyzed desymmetrization **3.145** was not found, we decided to consider other catalysts.

### *3.5.2 Development of Desymmetrization with Nickel Catalysts*

Since extensive efforts into the development of an asymmetric copper-catalyzed cross-coupling failed to yield an efficient desymmetrization, we turned our attention to nickel catalysts. Nickel has become one of the most popular metals for cross-couplings of alkyl electrophiles. Nickel can avoid some of the major issues associated with the cross-couplings of unactivated alkyl electrophiles, such as slow oxidative addition and risk of β-hydride elimination after oxidative addition.[76] Though β-hydride elimination is prevalent with palladium catalysts the energy of rotation around the Ni-C bond to form an agostic interaction prior to β-hydride elimination is often significantly higher in nickel than palladium, resulting in slower β-hydride elimination for nickel complexes.[77] Nickel is also

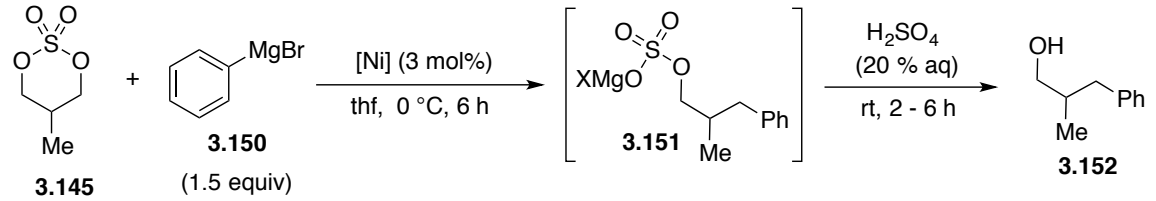
[76] For a review of Ni-catalyzed cross-coupling of unactivated alkyl halides see: Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525.
[77] Lin, B.; Liu, L.; Fu, Y.; Luo, S.-W.; Chen, Q.; Guo, Q.-X. *Organometallics*, **2004**, *23*, 2114.

a relatively electropositive metal, which helps to facilitate oxidative addition.[78] One of the other advantages of nickel, in some cases, is that several different catalytic cycles are accessible: Ni(I)/Ni(III), Ni(0)/Ni(II), and others where nickel remains at Ni(I) or Ni(II) through the entire cycle.[79]

We started our investigation of the use of nickel in the desymmetrization of cyclic sulfates using conditions developed by Kambe and co-workers for a Ni-catalyzed Kumada coupling of alkyl electrophiles (*vide supra*). These conditions seemed applicable for our system as mechanistic studies indicated a Ni(0)/Ni(II) cycle without the intermediacy of radical species. As a lead experiment, cyclic sulfate **3.145** was treated with phenyl magnesium bromide **3.150**, $Ni(cod)_2$ and isoprene (Table 3.3, entry 1) at 0°C in tetrahydrofuran. The cyclic sulfate underwent efficient cross-coupling and after acid hydrolysis alcohol **3.81** was obtained in 78% yield. Similar to what Kambe and co-workers observed, the reaction is much less efficient without the use of isoprene or diene additives (entry 2). However, the use of phosphine modified nickel catalysts did lead to low isolated yields of the desired product under the reaction conditions (entries 4, 5). Though isolated yields of the desired product were low during the catalyst screen, we anticipated that once a highly enantioselective chiral ligand was identified, yields could be improved by adjusting reaction conditions.

[78] Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature,* **2014**, *509*, 299.
[79] For a review on nickel-catalyzed cross-coupling mechanisms see: Hu, X.; *Chem. Sci.* **2011**, *2*, 1867.

**Table 3.3: Initial Results of the Nickel Catalyzed Desymmetrization of Cyclic Sulfate 3.145**

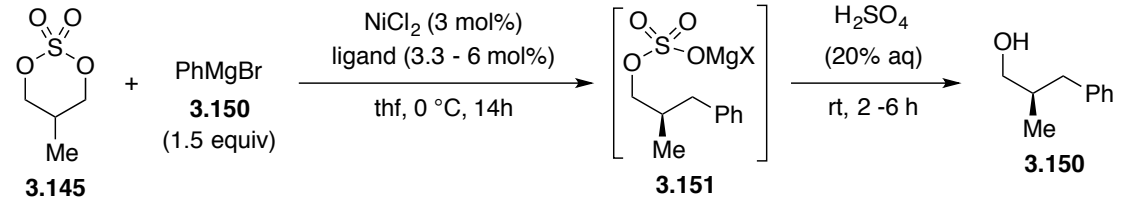


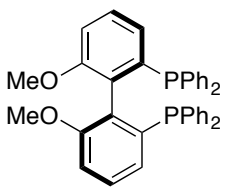

| entry | [Ni] | conv.[a] | yield |
|---|---|---|---|
| 1 | $Ni(cod)_2$ isoprene (10 mol%) | 100% | 78% |
| 2 | $Ni(cod)_2$ | 34% | nd |
| 3 | $NiCl_2$ | 46% | 19% |
| 4 | $Ni(PPh_3)_2Cl_2$ | 62% | 29% |
| 5 | $Ni(dppe)_2Cl_2$ | 85% | 22% |

[a] conversion determined by $^1H$ NMR analysis; nd: not determined.

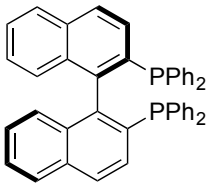
After we discovered that nickel can indeed catalyze the conversion of **3.145** to **3.81** *via* a Kumada coupling, finding a chiral ligand scaffold that could influence the enantioselectivity of the reaction became the focus (Table 3.4). Bidentate (**L3.32, L3.5, L3.21, L3.33**) and monodentate phosphine ligands (**L3.34, L3.35**) performed poorly in the reaction leading to moderate yields and low enantioinduction (Table 3.4). To our delight phenyl Pybox ligand **L3.31** gave the desired product in 75:25 er and 33% yield (Table 3.4, entry 8). The enantioselectivity of the reaction with **L3.31** could be further enhanced to 80:20 er using $Ni(cod)_2$ in place of $NiCl_2$.

**Table 3.4: Initial Chiral Ligand Screen for Desymmetrization of Cyclic Sulfate 3.145**

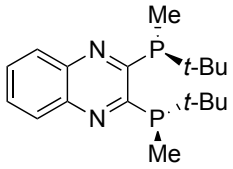


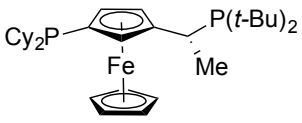

**L3.32**
< 5% y



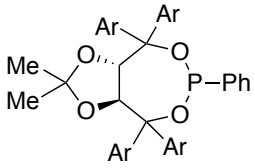

**L3.5**
48% y
50:50 er



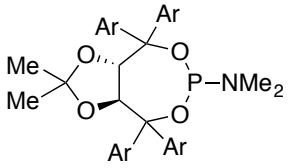

**L3.21**
< 5% y



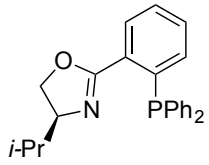

**L3.33**
23% y
51:49 er



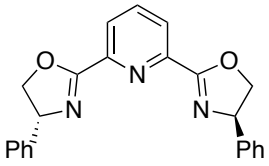

Ar= 3,5-*i*-$Pr_2C_6H_3$
**L34**
19% y
52:48 er




Ar= 3,5-*t*-$Bu_2C_6H_3$
**L35**
19% y
50:50 er




**L3.36**
5% y
52:48 er



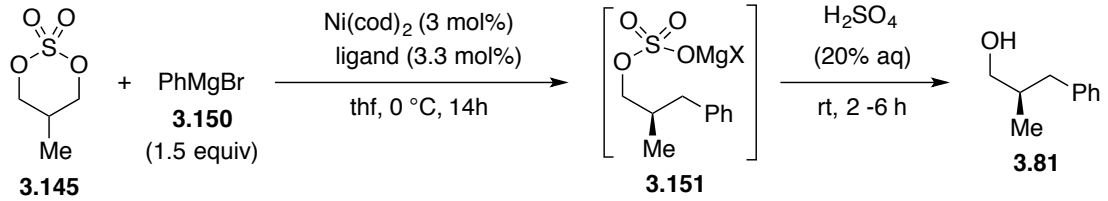

**L3.31**
38% y
75:25 er

[a] Reactions employed 0.3 mmol of **3.145**. [b] yield of purified product. [c] enantiomer ratios were determined by SFC analysis on chiral stationary phase.

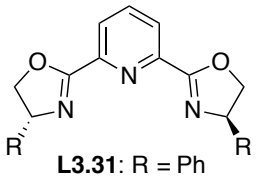
The rest of the ligand screen was focused on other bidentate and tridentate nitrogen based ligands with $Ni(cod)_2$ pre-catalyst, to learn if synthetically useful enantioselectivities could be observed (Table 3.5). Changing the substituent on the oxazoline ring of the PyBox ligand to aliphatic groups (**L3.31, L3.37**-**L3.39**) led to significantly diminished selectivities even with bulky groups, such as *t*-Bu (**L3.39**). These results indicate that the aromatic rings on the oxazoline are important for a highly selective reaction. It is also apparent that the position of the aromatic ring is highly important, evident by indane PyBox **L3.40** and benzyl PyBox **3.41** which both led to nearly

racemic product under the reaction conditions. The Box family of ligands also led to a relatively nonselective reaction, indicating that either tridentate coordination or sigma donating ability of the pyridyl ring is important (**L3.42, L3.43, L3.44**). To further probe the effect the pyridyl ring has on the reaction, PyBox derivatives **L3.45** and **L3.46** were synthesized. Addition of electron-donating dimethylamino group **L3.45** had little effect on the overall reaction while *p*-chloroPyBox **L3.46** lead to slightly lower enantioselectivity. However, in the case of **L3.46** we cannot rule out ligand modification during the reaction.

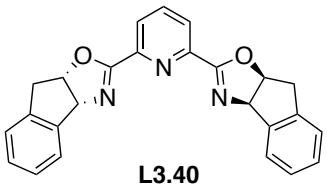
**Table 3.5: Ligand Screen of PyBox and Box Ligand Scaffolds**



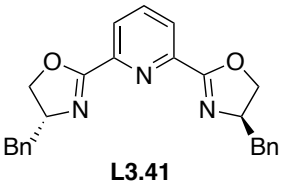

| | yield (%) | er |
|---|---|---|
| **L3.31** | 33 | 80:20 |
| **L3.37** | 62 | 56:44 |
| **L3.38** | 44 | 62:38 |
| **L3.39** | 33 | 54:46 |



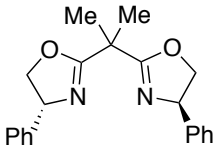
**L3.31**: R = Ph
**L3.37**: R = Me
**L3.38**: R = *i*-Pr
**L3.39**: R = *t*-Bu



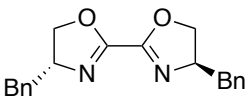
**L3.40**
49% y
51:49 er



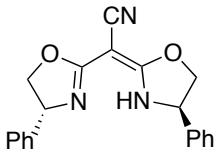
**L3.41**
59% y
56:44 er



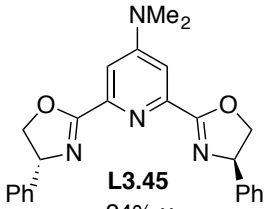
**L3.42**
41% y
50:50 er



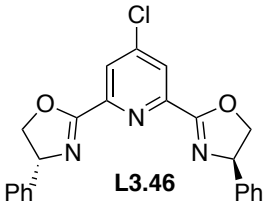
**L3.43**
43% y
59:41 er



**L3.44**
24% y
50:50 er



**L3.45**
24% y
79:21 er



**L3.46**
26% y
63:37 er

[a] Reactions employed 0.3 mmol of **3.145**. [b] yield of purified product. [c] enantiomer ratios were determined by SFC analysis on chiral stationary phase.

### *3.5.3 Synthesis of Pybox Ligands*

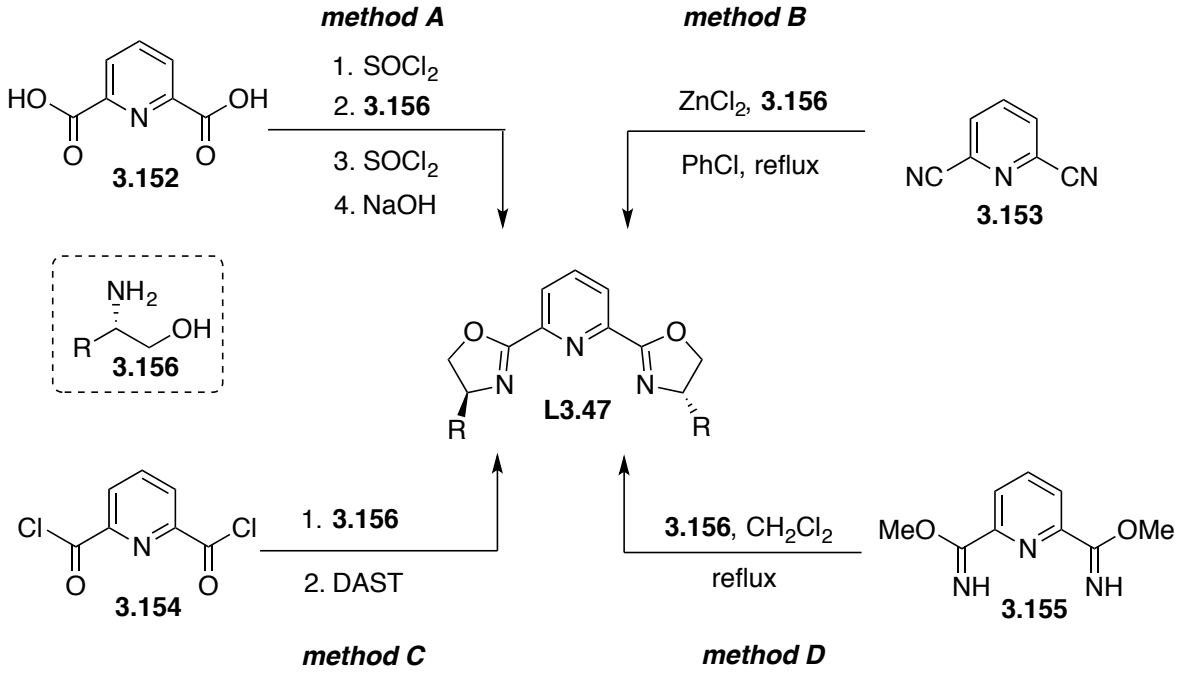
Since removal of the aromatic ring on the PyBox ligand led to low enantioselectivities, we proposed that perhaps modifying the aromatic ring of PhPyBox **L3.31** would lead to a ligand scaffold that would give an improved reaction. However, these types of PyBox ligands are not readily available. Nishiyama and co-workers were the first to synthesize Box ligands with a pyridine spacer, coined PyBox ligands in 1989.[80] Since then several PyBox derivatives have been synthesized and found to be highly selective ligands for a variety of transformations.[81] In general there are four routes used for the synthesis of PyBox ligands, all of which involve reaction of a chiral amino alcohol (**3.156**) with a pyridyl containing precursor (Scheme 3.33).[82]

[80] Nishiyama, H.; Kondo, M.; Nakamura, T.; Horihata, M.; Itoh, K. *Organometallics* **1989**, *8*, 846.

[81] For reviews on PyBox ligands see: (a) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119. (b) Johnson, J. S.; Evans, D. A.; *Acc. Chem. Res.* **2000,** *33*, 325. For a review on Box ligands see: Desimoni, G.; Faita, G.; Jorgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

[82] Tse, M. K.; Bhor, S.; Klawoon, M.; Anilkumar, G.; Jiao, H.; Dobler, C.; Spannenberg, A.; Magerlein, W.; Hugl, H.; Beller, M. *Chem. Eur. J.* **2006**, *12*, 1855.

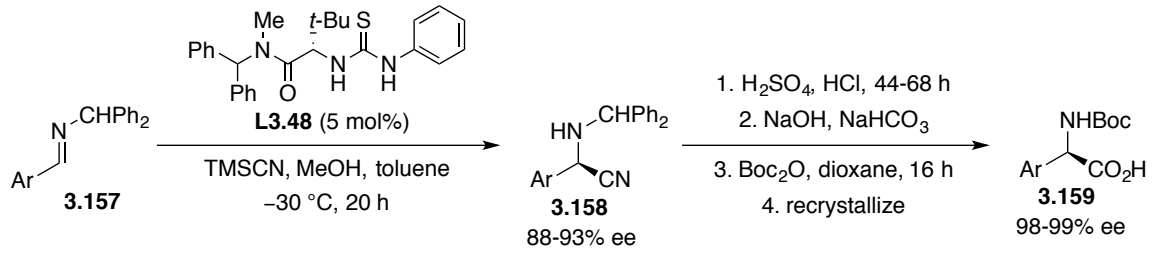
**Scheme 3.33: Different Methods for the Synthesis of PyBox Ligands**




For easily synthesized and commercial PyBox ligands, the chiral amino alcohols are derived from natural amino acids after reduction. However, in order to access PhPyBox derivatives the amino alcohols needed do not come from naturally occurring amino acids and therefore must be synthesized. There are several methods to synthesize unnatural α-amino acid derivatives, such as Jacobsen's catalytic asymmetric Strecker synthesis (Scheme 3.34).[83] In this method enantioselective addition of TMSCN to imines with a chiral thiourea catalysts yields addition product **3.158** in high yields and moderate ee. However, conversion of **3.158** to the desired amino acid **3.159** involves several functional group interconversions.

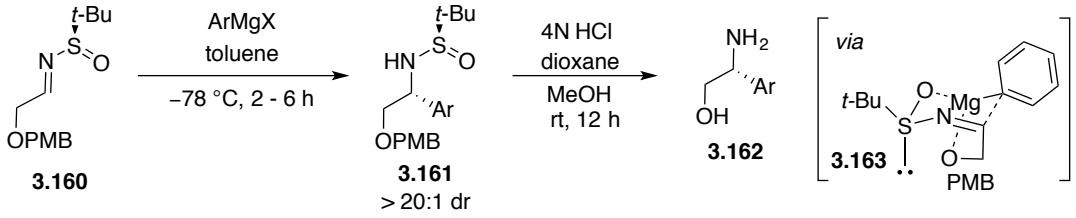
[83] Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968.

**Scheme 3.34: Jacobsen's Asymmetric Strecker Synthesis of Unnatural Amino Acids**




In order to quickly access a library of PyBox derivatives, we were interested in a more convergent method to the prepare amino alcohols where the diversity element is installed in a late stage. Ellman and co-workers[84] have developed a number of highly diastereoselective additions of nucleophiles to N-*tert*-butanesulfinyl imines, including additions of aromatic Grignard reagents to **3.160** (available in 3 steps from ethylene glycol) (Scheme 3.35).[85]

**Scheme 3.35: Synthesis of Amino Alcohols by Gringard Addition to Chiral Aldimines**



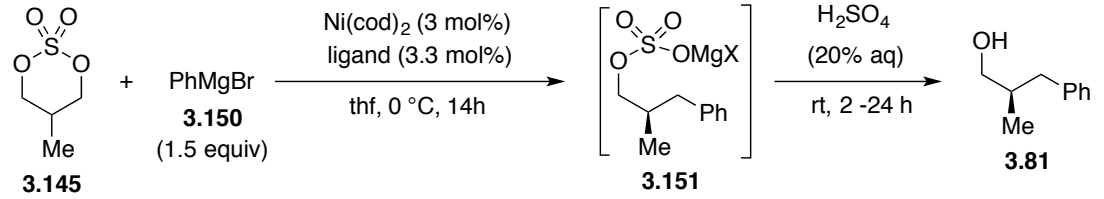

This reaction proceeds *via* six-membered cyclic transition state **3.163** with Mg coordination to both the sulfinyl oxygen and oxygen of the aldimine, resulting in excellent

[84] For a review on the use of Ellman's Auxilary see: Tang, T. P.; Owens, T. D.; Ellman, J. A. *Acc. Chem. Res.* **2002**, *35*, 984.

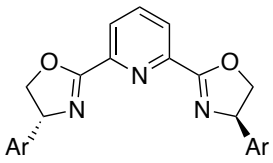
[85] (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (b) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883.

diastereoselectivites. The desired amino alcohols needed for the PyBox ligand syntheses are then available in one step by treatment of **3.161** with acid in protic solvent. Due to the convergent nature of the Ellman method, ease of preparation of the precursors, and high diastereoselectivites observed, this method was used to make a variety of optically pure amino alcohols. With the chiral amino alcohols in hand, a small library of ArPybox ligands (**L3.49** – **L3.58**, Table 3.6) was synthesized by condensation of enantioenriched amino alcohols with pyridyl diimidate **3.155** in dichloromethane (Method D, Scheme 3.33).

**Table 3.6: ArPyBox Ligands in Desymmetrization of Cyclic Sulfate 3.145**




| entry | ligand | Ar | yield[a] | er[b] |
|---|---|---|---|---|
| 1 | **L3.49** | 2-napthyl | 66% | 81:19 |
| 2 | **L3.50** | *o*-Cl | nd | 76:24 |
| 3 | **L3.51** | mesityl | 52% | 69:31 |
| 4 | **L3.52** | *p*-F | 61% | 73:27 |
| 5 | **L3.53** | *p*-OMe | 50% | 79:21 |
| 6 | **L3.54** | 3,5-$(OMe)_2C_6H_3$ | 60% | 80:20 |
| 7 | **L3.55** | 3,5-$Me_2C_6H_3$ | 72% | 87:13 |
| 8 | **L3.56** | 3,5-$Et_2C_6H_3$ | 50% | 92:8 |
| 9 | **L3.57** | 3,5-(*i*-Pr)$_2C_6H_3$ | 91% | 87:13 |
| 10 | **L3.58** | 3,5-(*t*-Bu)$_2C_6H_3$ | 53% | 86:14 |

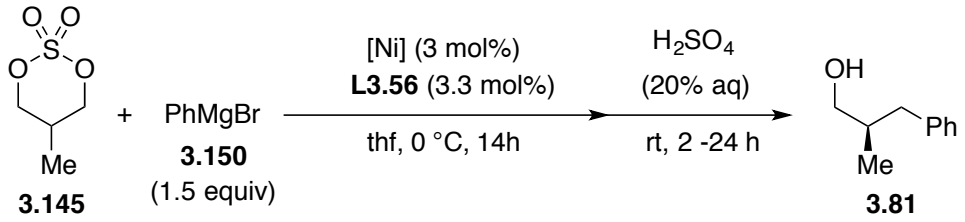



[a] yield of purified product. [b] enantiomer ratios were determined by SFC analysis on chiral stationary phase.

Through the screen of the small library of ArPyBox ligands it was discovered that increasing the steric bulk at the *meta* positions of the aromatic rings led to an increase in enantioselectivity in the reaction, while substitution at other positions led to decreases in selectivity or minimal change (Table 3.6). Using ArPyBox ligand **L3.56** with *meta*-ethyl groups led to the highest enantioselectivities observed. However, further increasing the size of the group to *i*-Pr or *t*-Bu did not lead to an enhancement in enantioselectivity and instead the selectivity dropped slightly (**L3.57**, **L3.58**).

With our optimal ligand in hand, we were interested in finding a less expensive, air-stable pre-catalyst to replace $Ni(cod)_2$. The use of halogen containing pre-catalysts led to lower enantioselectivities (Table 3.7, entries 2, 3) while $Ni(acac)_2$ gave comparable yields and enantioselectivities as $Ni(cod)_2$ (entry 6).

**Table 3.7: Use of Different Nickel Pre-Catalysts for Desymmetrization of 3.145**



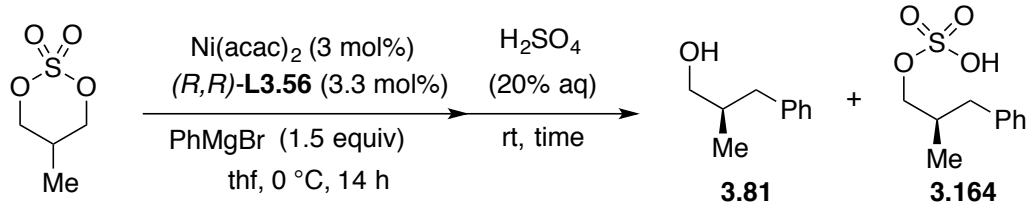

| entry | [Ni] | yield[a] | er[b] |
|---|---|---|---|
| 1 | $Ni(cod)_2$ | 50% | 92:8 |
| 2 | $NiBr_2$•diglyme | 87% | 86:14 |
| 3 | $NiCl_2$ | 34% | 87:13 |
| 4 | $Ni(OTf)_2$ | 43% | 64:36 |
| 5 | $Ni(OAc)_2$•$4H_2O$ | 88% | 80:20 |
| 6 | $Ni(acac)_2$ | 53% | 92:8 |

[a] yield of purified product. [b] enantiomer ratios were determined by SFC analysis on chiral stationary phase.

During the ligand and pre-catalyst screening it was determined that low isolated yields of **3.81** were due to incomplete hydrolysis of **3.151** to the desired alcohol. If the acid hydrolysis is stopped after 6 h, alcohol **3.81** is isolated in 64% yield along with sulfate half ester **3.164** in 17% yield (Table 3.8, entry 1). When the acid hydrolysis was left for 24 h

instead of 6 h, high isolated yields of the desired alcohol are obtained (Table 3.8, entry 2). We did not investigate the acid hydrolysis thoroughly, but increasing the concentration of the acid, heating the mixture or changing the nature of the acid could likely lead to a more efficient hydrolysis.

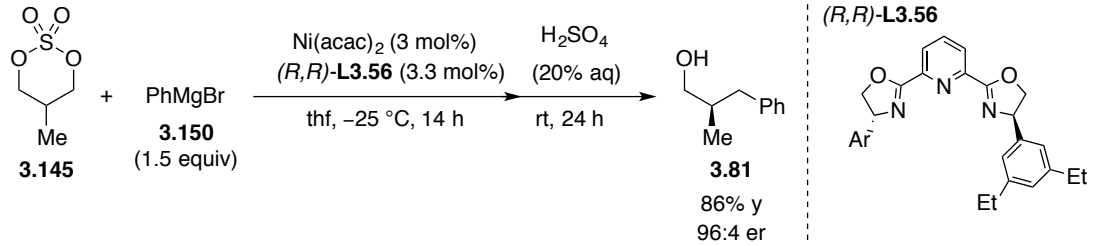
**Table 3.8: Optimization of Cyclic Sulfate Desymmetrization; Incomplete Conversion of 3.151**




| entry | time | yield **3.81** | yield **3.164** |
|---|---|---|---|
| 1 | 6 h | 64% | 17% |
| 2 | 24 h | 88% | nd |

A final screen of reaction conditions was preformed to see if the enantioselectivity of the reaction could be increased. Different solvents or mixtures with tetrahydrofuran did not result in increased enantioselectivities; surprisingly performing the reaction in $Et_2O$ did not furnish any of the desired product. To our delight, performing the desymmetrization of **3.145** with $Ni(acac)_2$ at lowered temperature ( -25 °C) resulted in a highly selective reaction (Scheme 3.36). Decreasing the temperature further to -50 °C gave no improvement in enantioselectivity and very low conversion after 24 h. With effective control over the enantioselectivity and yield of the desymmetrization, the scope of the nucleophile was investigated.

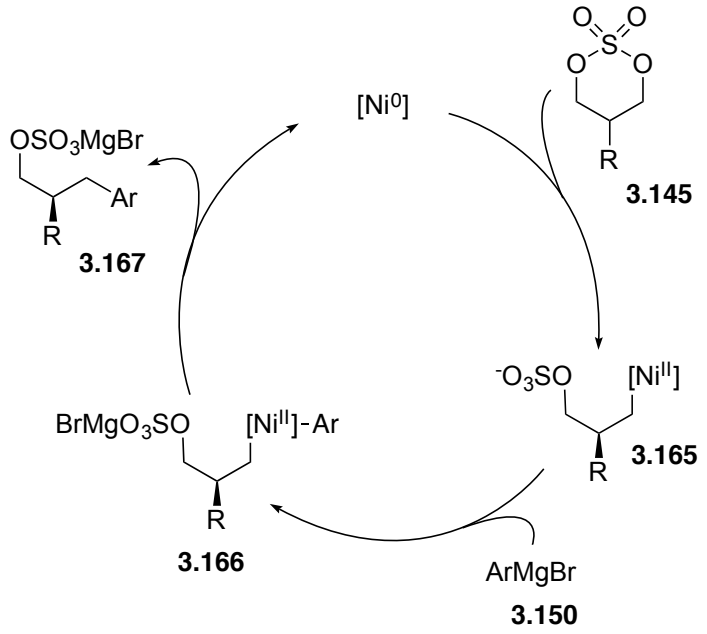
**Scheme 3.36: Optimized Conditions for Desymmetrization of Cyclic Sulfates**




### *3.5.4 Scope of the Nucleophile in Nickel Catalyzed Desymmetrization and Suppression of Byproducts*

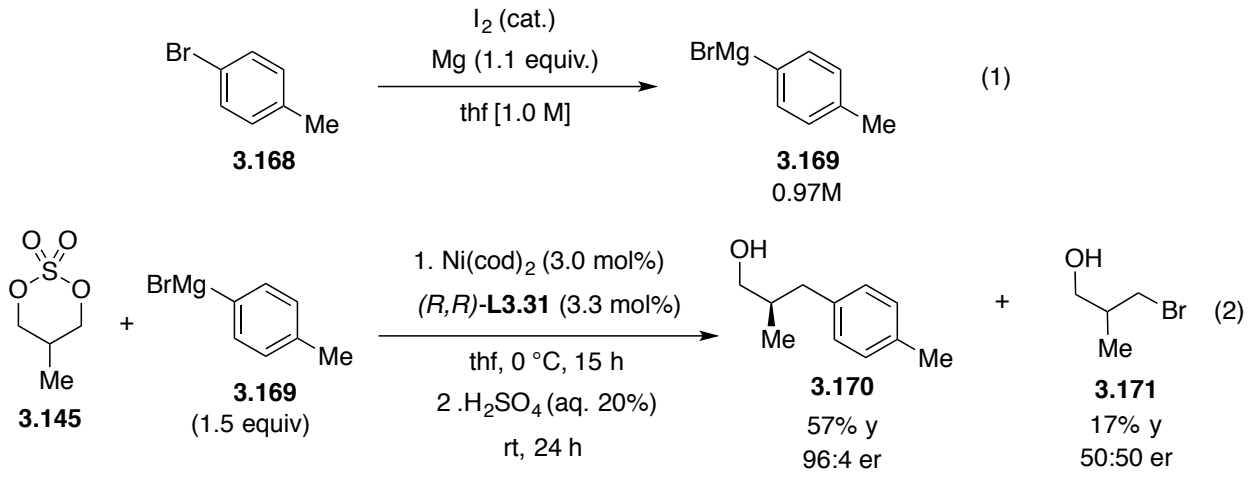
Our working mechanistic proposal was based on a classic Kumada cross-coupling cycle, in which a Ni(0) species (generated *in situ*) oxidatively adds to **3.145**, followed by transmetalation of the nucleophile **3.150** and subsequent reductive elimination to yield the product (Scheme 3.37). In this working proposal, oxidative addition (**3.145** to **3.165**) occurs prior to transmetalation (**3.165** and **3.166**) and is proposed to be the stereochemistry determining step.

**Scheme 3.37: Ni-Catalyzed Desymmetrization by Ni(0)/Ni(II) Cycle**




We had briefly investigated at the use of different Grignard reagents in the desymmetrization with **L3.31**. We predicted that the nature of the aromatic Grignard reagent would not influence the enantioselectivity because it is not involved in the stereochemistry-determining step. Preparation of *p*-tolylmagnesium bromide **3.169** by magnesium insertion to 4-bromotoluene using iodine to activate the magnesium gave the desired Grignard reagent in high yield (Scheme 3.38, eq. 1). Replacing PhMgBr **3.150** with **3.169** in the desymmetrization resulted in low isolated yield, low enantioselectivity and formation of racemic brominated byproduct **3.171** in 17% yield (Scheme 3.38, eq. 2).

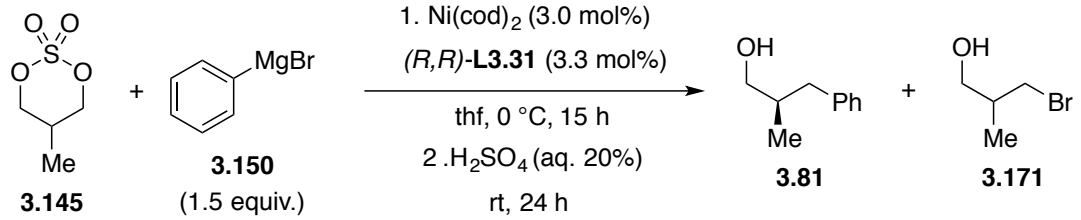
**Scheme 3.38: Initial Result of Grignard Reagent 3.169 in Desymmetrization**




Having made very little change in the steric and electronic nature of the nucleophile the drop in selectivity was surprising. We were interested in determining if the drop in enantioselectivity is a consequence of a different Grignard reagent or had something to do with formation of **3.171**, which had not been observed during screening.

An important difference between the Grignard reagents **3.169** and **3.150** is their sources. PhMgBr used during screening was purchased from Aldrich and **3.169** was prepared as noted above. Perhaps the use of an "aged" Grignard reagent was important for avoiding byproduct formation and promoting a highly selective reaction. To test this, **3.150** was synthesized by Mg insertion (Scheme 3.38, eq. 1) and used in the desymmetrization reaction the same day (Table 3.9, entry 2). In a second experiment the freshly prepared **3.150** was allowed to stand at 2-8 °C for 24 h and used again in the reaction (entry 3).

**Table 3.9: Comparison of Grignard Reagent Sources**

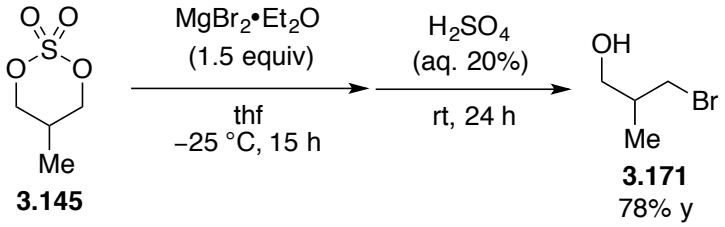



| source **3.150** | yield **3.81** | yield **3.171** | er |
|---|---|---|---|
| Aldrich | 78 | -- | 80:20 |
| "fresh" | 58 | 23 | 75:25 |
| "aged" | 76 | -- | 81:19 |

It is apparent that indeed allowing the Grignard reagent to age suppresses byproduct formation and gives the expected enantioselectivity. When using "fresh" PhMgBr (**3.150**) enantioselectivity was lowered and brominated byproduct **3.171** is formed in 23% yield. When the Grignard reagent is allowed to age, precipitatation of magnesium salts occurs before the supernatant is used in the reaction. We expected excess magnesium salts, such as $MgBr_2$, in solution before "aging" could also lead to this byproduct formation.[86] Indeed subjecting **3.145** to reaction with $MgBr_2 \bullet Et_2O$ led to 78% yield of brominated byproduct **3.171** (Scheme 3.39). This is consistent with formation of **3.171** not involving a chiral nickel catalyst. Attempts to suppress the byproduct formation through use of halide-free nucleophiles as $Ph_2Mg$ or $Ph_2Zn$ led to no conversion of the starting material.

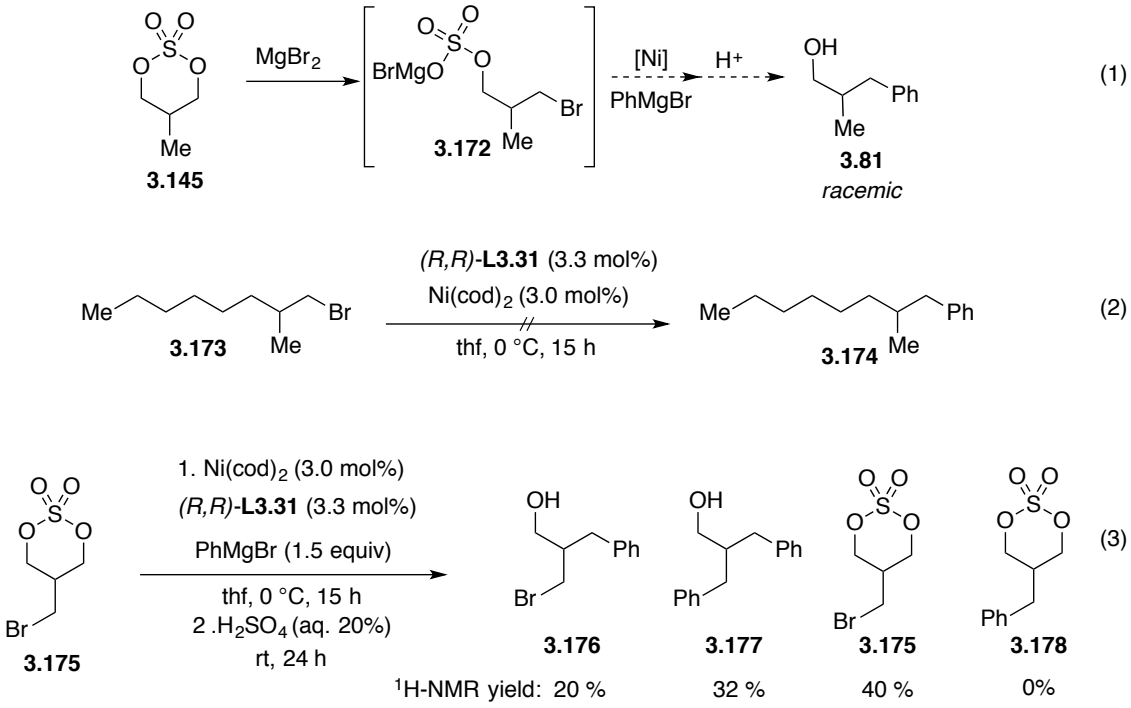
[86] K.C. Cannon, G.R. Krow, in: G.S. Silverman, P.E. Rakita (Eds.), *Handbook of Grignard Reagents,* Marcel Dekker, New York, **1996**, pp. 271–289.

**Scheme 3.39: Formation of 3.171 by $MgBr_2$ Ring Opening**




Since cyclic sulfate **3.145** can undergo non-selective ring opening to **3.172** without the aid of a catalyst, we worried that intermediate **3.171** might participate as an electrophile in a Kumada coupling under the reaction conditions (Scheme 3.40, eq. 1). Several groups have shown non-activated alkyl bromides can undergo efficient cross-coupling reactions in the presence of Ni (*vide supra*). Since **3.172** is formed in a racemic fashion, this would then lead to racemic product **3.81** and an overall decrease in enantioselectivity in the reaction (Scheme 3.40, eq. 1). In order to test this hypothesis, alkyl bromide **3.173** was synthesized and subjected to the reaction conditions developed for the desymmetrization. Unfortunately, none of the desired cross-coupled product was observed (Scheme 3.40, eq. 2). Alkyl bromide **3.173** is not a perfect model for intermediate **3.172** and perhaps the sulfate group aids in the cross-coupling. This idea was tested by subjecting brominated cyclic sulfate **3.175** to cross-coupling conditions; indeed, bis-coupled product **3.177** was formed, confirming that alkyl bromides can act as electrophiles under the reaction conditions (Scheme 3.40, eq.3). The products observed in the reaction also support the importance of the sulfate arm in the cross-coupling as no **3.178** was observed.

**Scheme 3.40: Testing Origins of Diminished Enantioselectivity in Ni-Catalyzed Desymmetrization**

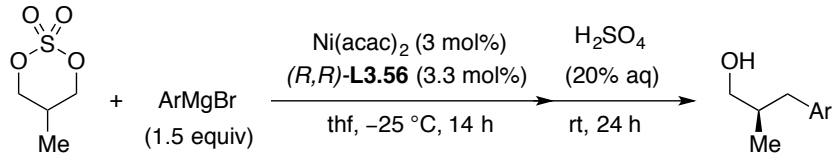



Through the series of experiments above, we have shown that a possible explanation for diminished enantioselectivity in the desymmetrization with unaged Grignard reagents is due to a magnesium bromide opening of **3.145** followed by Kumada coupling. We cannot rule out other possibilities such as Lewis acid activation of the cyclic sulfate by $MgBr_2$, which alters the transition state. At this point it is known that for a highly selective reaction, the Grignard reagent must sit to allow precipitation of magnesium salts before use.

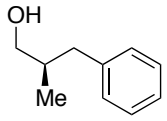
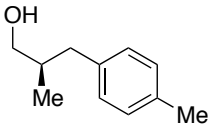
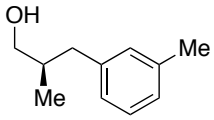
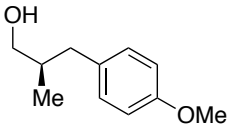
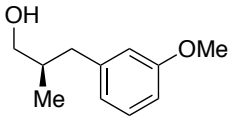
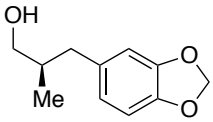
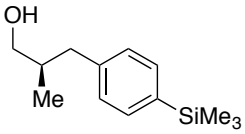
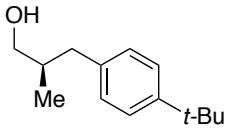
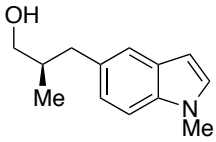
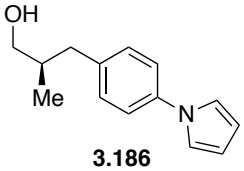
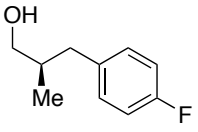
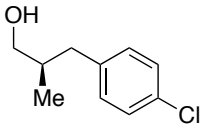
With the aging process in mind, we moved forward to investigating the scope of the nucleophiles in the optimized desymmetrization with **L3.56** (Table 3.10). Using the optimized nucleophile preparation, p-tolylmagnesium bromide furnishes the desired product **3.170** in excellent yield and 95:5 er without the presence of brominated

byproduct. Other aromatic Grignard reagents with electron-donating groups also lead to high yields and enantioselectivities (**3.179**, **3.180**, **3.184**). The desymmetrization also tolerates silyl groups and protected heterocycles on the nucleophile, while halogenated containing nucelophiles give slightly lower selectivities and yields, even when employing higher catalyst loadings (**3.187**, **3.188**). The lower yields in these cases is due to formation of **3.171**, perhaps the electron-deficient nucleophiles are slower to transmetalate, which allows for competitive ring-opening.

**Table 3.10: Scope of Nucleophiles in Nickel-Catalyzed Desymmetrization**




**3.145**

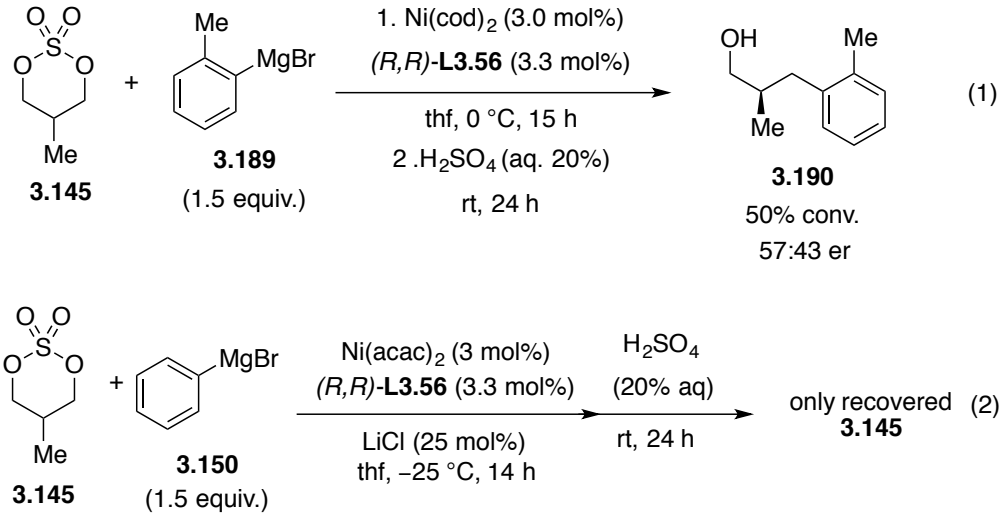
| | | | |
|---|---|---|---|
|  |  |  |  |
| **3.81**<br>96:4 er<br>88% y | **3.170**<br>95:5 er<br>98% y | **3.179**<br>95:5 er<br>83% y | **3.180**<br>95:5 er<br>80% y |
|  |  |  |  |
| **3.181**<br>89:11 er<br>86% y | **3.182**<br>94:6 er<br>81% y | **3.183**<br>91:9 er<br>93% y | **3.184**<br>96:4 er<br>90% y |
|  |  |  |  |
| **3.185**<br>95:5 er<br>52% y | **3.186**<br>95:5 er<br>44% y | **3.187**[b]<br>93:7 er<br>52% y | **3.188**[b]<br>92:8 er<br>59% y |

Reactions employed 0.3 mmol of cyclic sulfate and 1.5 equiv of ArMgBr in thf. Results are an average of two experiments. Yield represents isolated yield after purification by silica gel chromatography. Enantiomer ratios were determined by SFC analysis on chiral stationary phase. [b]Reaction run with 6.0% $Ni(acac)_2$ and 6.6% **L3.56**

Unfortunately, *ortho*-substituted Grignard reagents are slow to react under the optimized conditions at -25 °C, and at slightly higher temperatures lead to low enantioselectivities (Scheme 3.41, eq. 1). Attempts to use nucleophiles with sensitive

functional groups, synthesized using methods developed by Knochel and co-workers,[87] failed in the reaction. Further investigations revealed that addition of lithium chloride salts to a reaction with PhMgBr **3.150** had a detrimental effect on the reaction (Scheme 3.41, eq. 2). Extensions of this method to include vinyl and alkyl nucleophiles will be discussed in detail later.

**Scheme 3.41: Examples of Failed Desymmetrization Reactions**

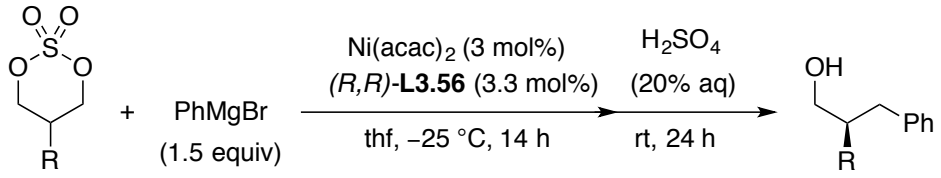


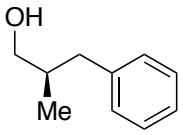

### *3.5.5 Scope of Cyclic Sulfates in Nickel Catalyzed Desymmetrization*

[87] (a) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed*. **2004**, *43*, 3333. (b) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett*. **2004**, 6. 4215. (c) Ren, H.; Krasovskiy, A.; Knochel, P. *Chem. Comm*. **2005**, 543. (d) Liu, C-Y.; Knochel, P. *Org. Lett*. **2005**, *7*, 2543. (e) Ren, H.; Knochel, P. *Chem. Comm*. **2006**, 726. (f) Sinha, P.; Knochel, P. *SynLett* **2006**, *19*, 3304. (f) Liu, C.-Y.; Ren, H.; Knochel, P. *Org. Lett*. **2006**, *8*, 617.

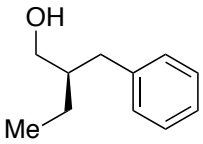
Having extended the desymmetrization method to include various aromatic Grignard reagents, our focus turned to extending the reactions to cyclic sulfates other than **3.145**. Several substituted cyclic sulfates were synthesized and subjected to cross-coupling with PhMgBr (Table 3.11). The desymmetrization proceeded smoothly with cyclic sulfates bearing larger alkyl substituents, maintaining high yields and enantioselectivity (**3.191**, **3.192**). Cyclic sulfates bearing pendant aromatic rings furnished the desired product under the reaction conditions with moderate levels of enantioselectivity and yield (**3.193**, **3.194**). Even cyclic sulfates with a protected alcohol was tolerated in the reaction yielding **3.195** in synthetically useful yield and enantioselectivity.

**Table 3.11: Application of Ni-Catalyzed Desymmetrization to Substituted Cyclic Sulfates**

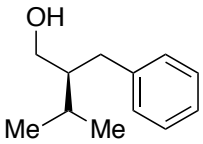


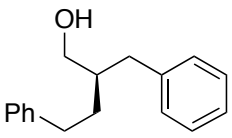

**3.81**
96:4 er
88% y



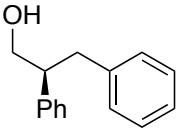

**3.191**
96:4 er
85% y



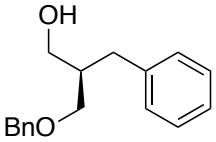

**3.192**
95:5 er
83% y




**3.193**
88:12 er
63% y




**3.194**
86:14 er
54% y




**3.195**
93:7 er
81% y

Reactions employed 0.3 mmol of cyclic sulfate and 1.5 equiv of ArMgBr in thf. Results are an average of two experiments. Yield represents isolated yield after purification by silica gel chromatography. Enantiomer ratios were determined by SFC analysis on chiral stationary phase.

In order to demonstrate the synthetic utility of the Ni-catayzed asymmetric Kumada cross-coupling, the reaction was performed with one gram of **3.145** with isolation of sulfate half-ester **3.164** (Scheme 3.42, eq. 1). Alkyl sulfates, such as **3.164**, are known

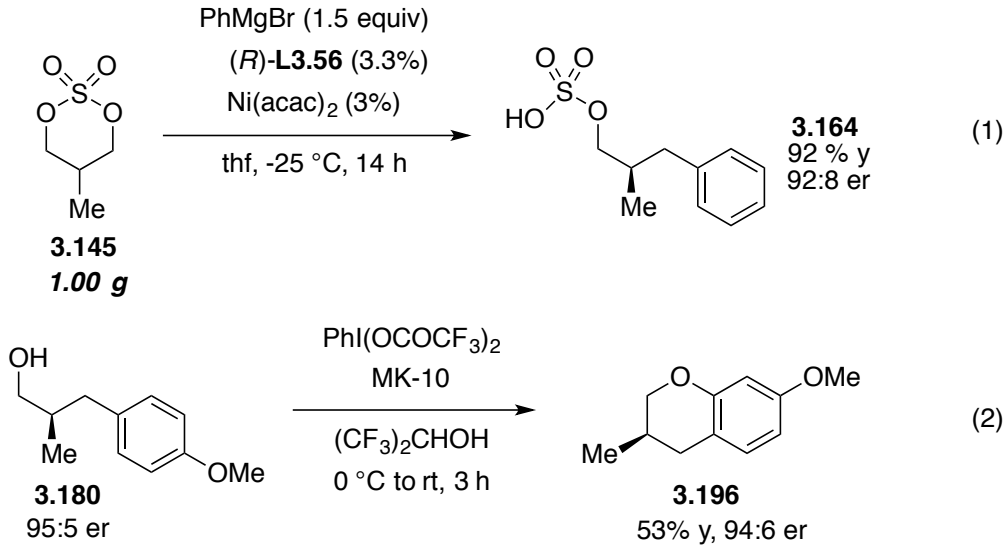
to undergo a variety of substitution reactions with sulfides and amines.[88] Though the enantioselectivity of the large scale coupling is slightly diminished, this could be resolved by a slower addition of the aromatic Grignard reagent. To demonstrate the utility of the product formed by the desymmetrization, alcohol **3.180** was transformed in to substituted chroman **3.196** by oxidation with phenyliodine(III) bistrifluoroacetate (Scheme 3.42, eq. 2).[89] Substituted chromans like **3.196**, are core structures in a number of different biologically active natural products.[90]

[88] For examples of substitution of alkyl sulfates see: (a) Itoh, S.; Hirai, T.; Totsuka, Y.; Takagi, H.; Tashiro, Y.; Wada, K.; Wakabayashi, K.; Shibutani, S.; Yoshizawa, I. *Chem. Res. Toxicol.* **1998**, *11*, 1312. (b) Fraser, A. S.; Kawasaki, A. M.; Jung, M. E.; Manoharan, M. *Tetrahedron Lett***. 2000**, *41*, 1523. (c) Prakash, T. P.; Manoharan, M.; Fraser, A. S.; Kawasaki, A. M.; Lesnik, E. A.; Owens, S. R. *Tetrahedron Lett.* **2000**, *41*, 4855. (d) Fuhrmann, H.; Grassert, I.; Holzhüter, G.; Grüttner, C.; Oehme, G. *New J. Chem.* **2002**, *26*, 1675. (e) MacKay, J. A.; Vedejs, *E. J. Org. Chem*. **2006**, *71*, 498.

[89] For cyclization method see: Hata, K.; Hamamoto, H.; Shiozaki, Y.; Caemmerer, S. B.; Kita, Y. *Tetrahedron* **2007**, *63*, 4052

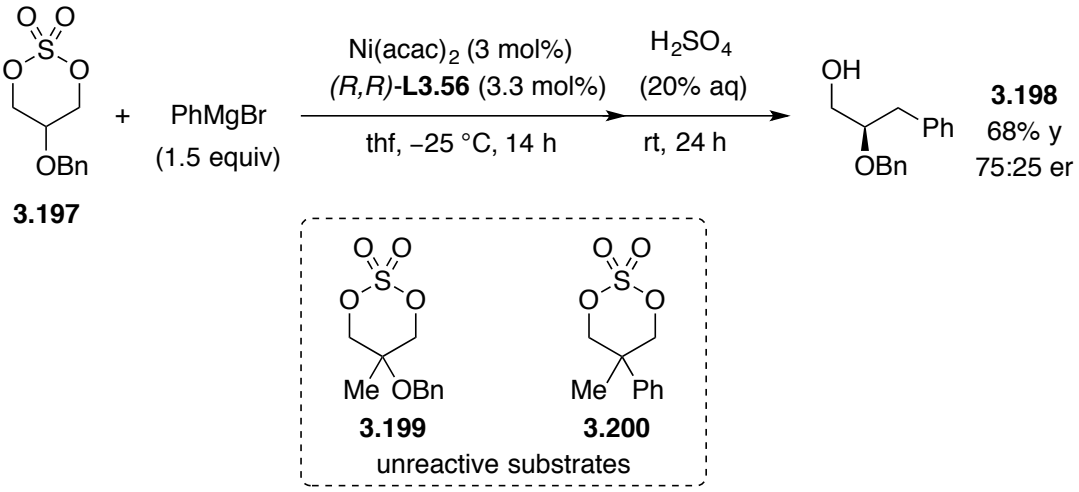
[90] (a) Cristau, P.; Vors, J.-P.; Zhu, J. *Tetrahedron* **2003**, *59*, 7859. (b) Pitsinos, E. N.; Vidali, V. P.; Couladouros, E. A. *Eur. J. Org. Chem.* **2011**, *2011*, 1207.

**Scheme 3.42: Synthetic Utility of Ni-Catalyzed Desymmetrization of Cyclic Sulfates**




All the examples in Tables 3.10 and 3.11 are limited to the synthesis of tertiary carbon stereocenters and in order to demonstrate the utility of this method we were interested in using the desymmetrization to access heteroatom and quaternary stereocenters. Protected-alcohol containing cyclic sulfate **3.197** engaged in the asymmetric Kumada coupling affording monoprotected diol **3.198** in good yield with moderate enantioselectivity (Scheme 3.43). Though the enantioselectivity was diminished for the heteroatom containing cyclic sulfate **3.197**, this is the first example of extending the method to such systems and the enantioselectivity could likely be improved through ligand or condition screening. Disubstituted cyclic sulfates such as **3.199** or **3.200** did not participate in the cross-coupling reaction even at elevated temperatures (40 °C)(Scheme 3.43).

**Scheme 3.43: Desymmetrization of Cyclic Sulfates to Synthesize Heteroatom and Quaternary Stereocenters**

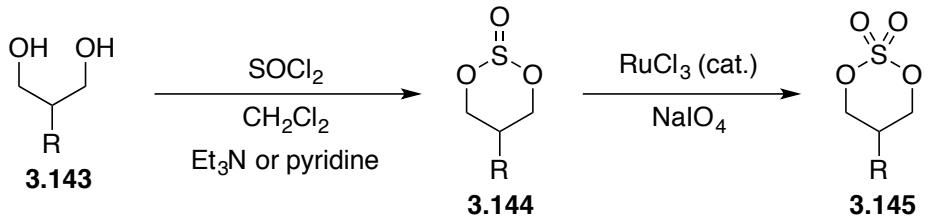



Unfortunately, extension of the asymmetric Kumada coupling to cyclic sulfates containing sensitive functional groups or other heteroatoms is hindered by the harsh oxidant used in the synthesis of the cyclic sulfates. The synthesis of cyclic sulfates is usually performed in a two-step procedure from readily available diols (Scheme 3.44). Cyclization of the diol with thionyl chloride in the presence or absence of base yields the cyclic sulfite **3.144** which is then oxidized to the cyclic sulfate **3.145**. Though ruthenium trichloride with sodium periodate is typically used there are several other oxidants that can transform **3.144** to **3.145** including potassium permanganate[91], calcium permanganate,[92] and sulfuryl dichloride.[93] These reagents are all harsh oxidants and in

[91] (a) Edmundson, R. S. *Tetrahedron* **1964**, *20,* 2781. (b) Berridge, M. S.; Franceschini, M. P.; Rosenfeild, E.; Tewson, T. J. *J. Org. Chem.* **1990**, *55*, 1211.
[92] Lloyd, E. J.; Porter, Q. N. *Aust. J. Chem.* **1977**, *30*, 569.
[93] (a) Tewson, T. J. *J. Org. Chem*. **1983**, *48*, 3507. Miniami, K.; Nomura, T. *Chem. Pharm. Bull.* **1982**, *30*, 3106.

order to synthesize cyclic sulfates bearing alkynes, alkenes, etc., a new synthetic strategy must be applied.

**Scheme 3.44: Synthesis of Cyclic Sulfates from 1,3-Diols**

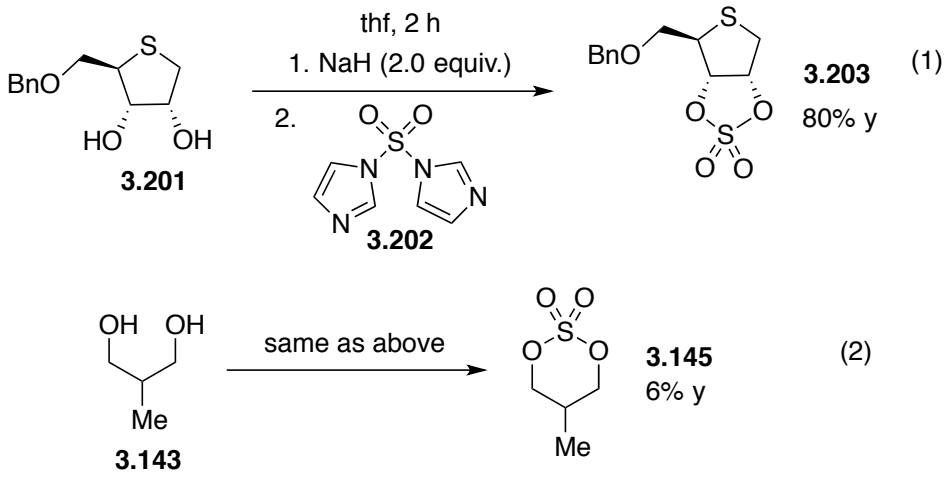



### *3.5.6 Synthesis of Cylic Sulfates*

There are a few one step methods to synthesize cyclic or acyclic sulfates such as **3.145**. Sulfonyldiimidazole **3.202** has been used previously in the synthesize of 5-membered cyclic sulfate **3.203** from 1,2-diol **3.201** (Scheme 3.45, eq. 1).[94] However, this strategy has never been applied to an acyclic 1,3-diol and attempts to apply this strategy in the synthesis of **3.145** failed to give high yields (Scheme 3.45, eq. 2).

[94] (a) Voigtlander, D.; Sander, M.; Harre, M. Proccess For Preparing Substituted 1-O-Acyl-2-Deoxy-2-Fluoro-4-Thio-β-D-Arabinofuranoses. U.S. Patent WO2010JP72182 20101203, June 23, 2011. (b) Fevig, T. L.; Mao, M. K.; Katzenellenbogen, J. A. *Steroids* **1995**, *51*, 471.

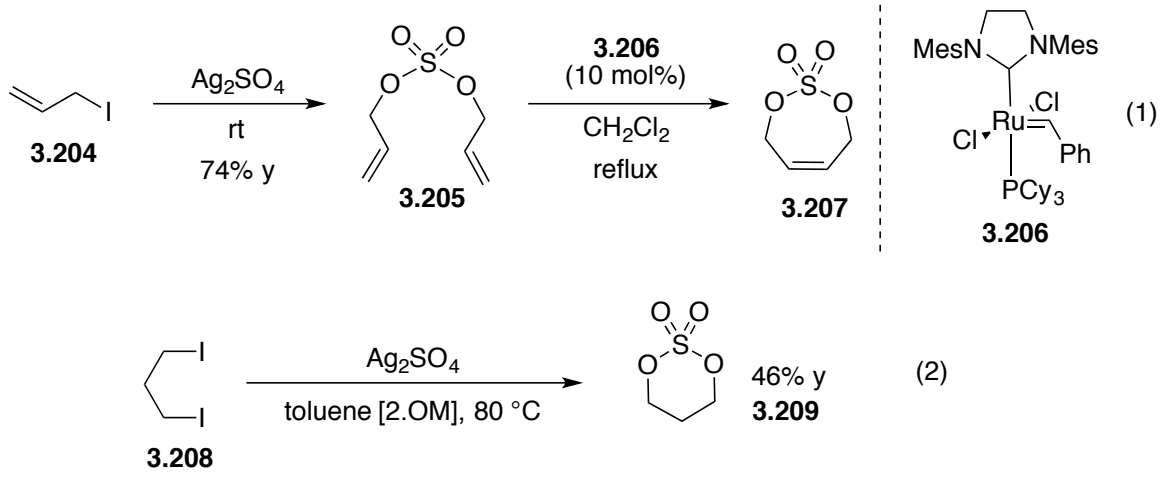
**Scheme 3.45: Synthesis of Cyclic Sulfates with $Im_2SO_2$**




Cyclic sulfate **3.207** has previously been synthesized *via* ring-closing metathesis of **3.205** with Grubbs second generation catalyst.[95] The acyclic substrate **3.205** was prepared from a reaction of allyl iodide with stoichiometric silver sulfate (Scheme 3.46, eq. 1). This strategy has not been applied to tethered 1,3-diols but the mild conditions used make this strategy appealing. Commercially available 1,3-iodopropane **3.208** was used to probe application of this method. After some screening, it was discovered that the reaction conducted at 2.0 M in toluene at 80 °C for 12 h gave **3.209** in 46% yield (Scheme 3.46, eq. 2). However, the use of these conditions to form **3.145** through this method failed to give the desired cyclic sulfate.

[95] Karsch, S.; Freitag, D.; Schwab, P.; Metz, P. *Synthesis* **2004**, *10*, 1696.

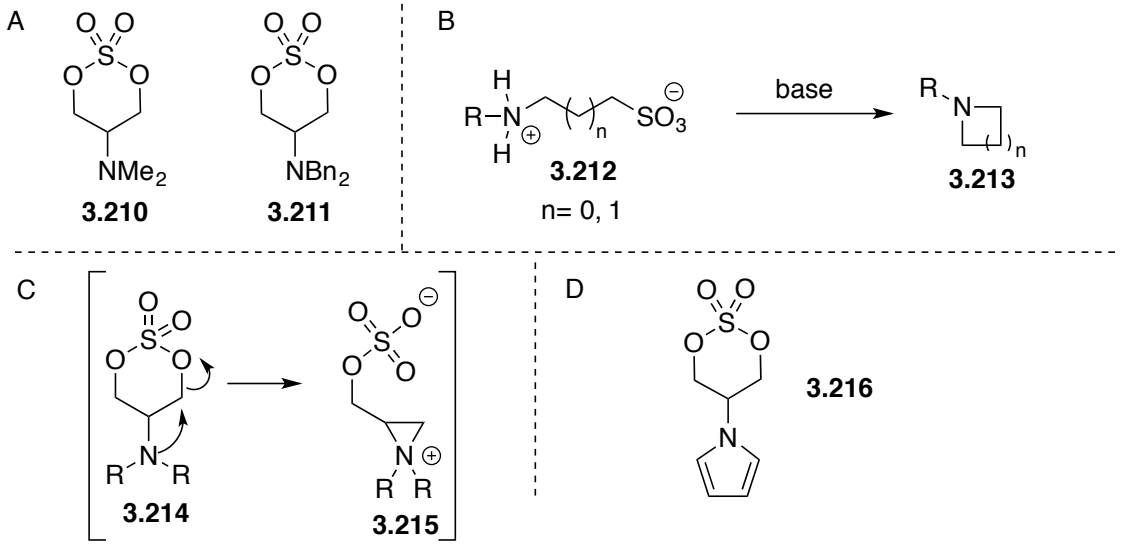
**Scheme 3.46: Synthesis of Cyclic Sulfates from Alkyl Iodines**




Though more mild conditions for the synthesis of 6-membered cyclic sulfates were not discovered through these attempts, further optimization of the two systems described could eventually offer alternative strategies. Synthesis of cyclic sulfates with nitrogen functionality on the ring may not be possible to access regardless of conditions used. Attempts to synthesize nitrogen substituted cyclic sulfates **3.210** and **3.211** all failed during the oxidation, possibly due to intramolecular ring opening (Scheme 3.47, A). In a modifications of the Wenker synthesis, aziridines[96] and azetidines[97] have been shown to be synthesized from tethered aminosulfonates in an intramolecular ring closure (Scheme 3.47, B). Perhaps, upon oxidation, an irreversible intramolecular ring-opening occurs which prohibits isolation of the desired cyclic sulfate (Scheme 3.47, C).

[96] (a) Olofsson, B.;Wijtmans, R.; Somfai, P. *Tetrahedron*, **2002**, *58*, 5979. (b) Li, X.; Chen, N.; Xu, J. *Synthesis*, **2010**, 3315.
[97] Burkett, B. A.; Ting, S. Z.; Gan, G. C. S.; Chai, C. L. L. *Tetrahedron* **2009**, *51*, 6590.

**Scheme 3.47: Synthesis of Nitrogen Substituted Cyclic Sulfates**

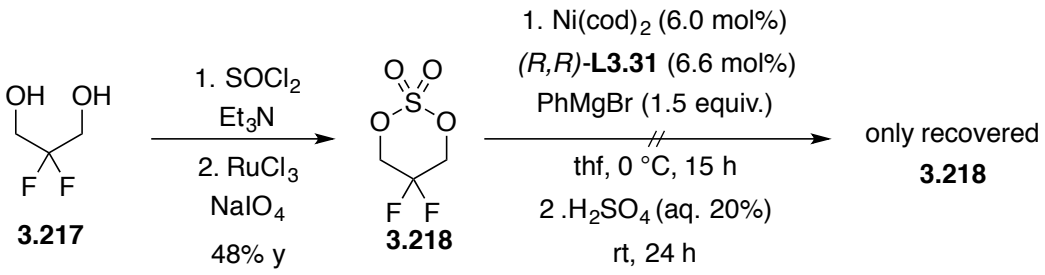



One proposed method to circumvent this type of decomposition pathway is to use nitrogen protecting groups which render the nitrogen lone-pair non-nucleophilic. The only attempt made to test this hypothesis was to synthesize **3.216** (Scheme 3.47, D). In this case the nitrogen lone pair should be non-nucleophilic as it is part of the aromatic system. However, oxidation of the sulfite in this case also led to decomposition. In this case failure to obtain **3.216** upon oxidation could be due to oxidation of the pyrrole and not intramolecular ring opening.[98] If synthesis of a nitrogen substituted cyclic sulfate were possible, then the asymmetric Kumada coupling developed would result in important enantioenriched unnatural phenylalanine derivatives.

[98] For a book containing information on the oxidation of pyrroles see: Jones, A. R.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: San Fransisco, 1977. p 235.

The synthesis of brominated and chlorinated cyclic sulfates is also complicated by the inability to access the precursor diols.[99] However, commercially available difluorinated diol **3.217** was used to synthesize cyclic sulfate **3.218**. Unfortunately, cyclic sulfate **3.218** did not undergo nickel-catalyzed cross-coupling with phenylmagnesium bromide even at higher catalyst loadings (Scheme 3.48).

**Scheme 3.48: Synthesis and Use of Halogenated Cyclic Sulfates in Kumada Coupling**



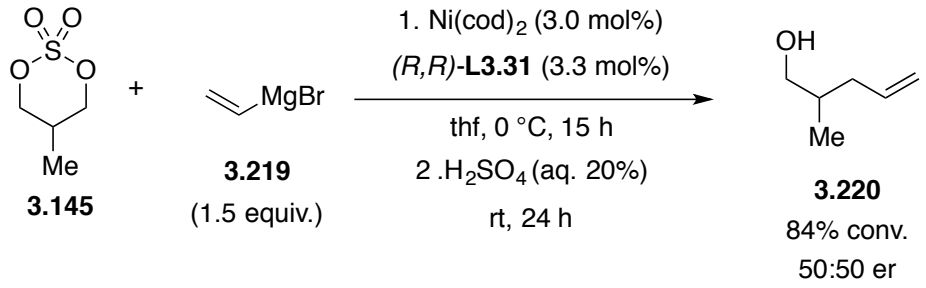

To expand the current scope of the Ni-catalyzed desymmetrization of cyclic sulfates, new methods to synthesize cyclic sulfates under milder conditions from different precursors need to be developed. Until then, the true scope of the cross-coupling method cannot be fully realized. However, in order to diversify the products obtained in the asymmetric Kumada coupling we were interested in expanding the scope of the nucleophile to include vinyl, alkyl, and allyl Grignard reagents.

### *3.5.7 Application of Desymmetrization to Other Grignard Reagents*

[99] Epoxide ring formation is the major product when reducing the halomalonates.

Initial efforts to employ different types of nucleophiles were aimed at the cross-coupling of vinyl Grignard reagents, due to their similarity in structure to ArMgBr and their synthetic utility. Nickel-catalyzed desymmetrization of **3.145** with vinylmagnesium bromide **3.219** in the presence of (*S*)-**L3.31** in tetrahydrofuran at 0 °C resulted in 84% conversion of the cyclic sulfate (Scheme 3.49). However significant amounts of brominated byproduct **3.171** were observed and the desired product **3.220** was determined to be racemic.[100] Formation of **3.220** was not observed without a nickel catalyst. The product formed may come exclusively from background cross-coupling of the intermediate bromide resulting from ring opening (*vide supra*).

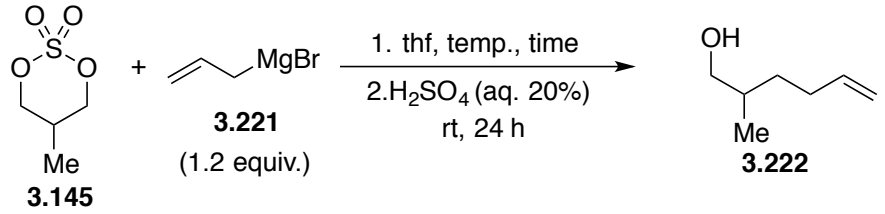
**Scheme 3.49: Desymmetrization of Cyclic Sulfate with Vinylmagensium Bromide**




Allyl Grignard reagents are also not applicable in the Ni-catalyzed asymmetric Kumada couplings. Ring opening of **3.145** in the absence of a nickel catalyst to **3.222** is significant, with 20% conversion to **3.222** observed at -78 °C (Table 3.12).

[100] The optical purity of **3.220** was determined by Mosher ester analysis.

**Table 3.12: Cyclic Sulfate Ring Opening by Allylmagnesium Bromide**




| entry | temp | time | conv.[a] |
|---|---|---|---|
| 1 | rt | 14 h | 100% |
| 2 | 0 °C | 14 h | 100% |
| 3 | -78 °C | 20 h | 20% |

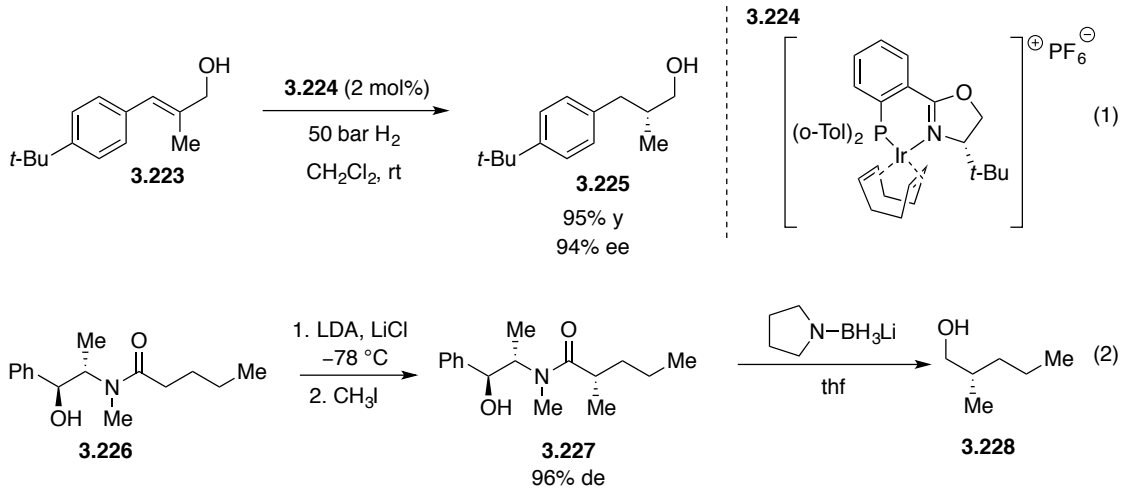
[a] conversion determined by $^1$H-NMR analysis

Aliphatic Grignard reagents in the desymmetrization may be the most useful class of nucleophiles for this method. The Ni-catalyzed desymmetrization of cyclic sulfates with aryl Grignard reagents yields products which can be easily synthesized via asymmetric Ir- and Rh-catalyzed hydrogenation of substituted allylic alcohol derivatives such as **3.223** (Scheme 3.50, eq. 1).[101] However, if alkyl nucleophiles were implemented in the asymmetric Kumada coupling, this would be a catalytic enantioselective method to access products like **3.228**. These types of products are still commonly synthesized *via*

[101] For selected examples see: (a) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878. (b) Dieguez, M.; Mazulea, J.; Pamles, O.; Verendel, J. J.; Anderson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 7208. (c) Spindeler, F.; Malan, C.; Lotz, M.; Kesselgruber, M.; Pittelkow, U.; Rivas-Nass, A.; Briel, O.; Hans-Urlich, B. *Tetrahedron: Asymm.* **2004**, *15*, 2299. (d) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2897.

diastereoselective enolate alkylations using stoichiometric chiral auxiliaries (Scheme 3.50, eq. 2).[102]

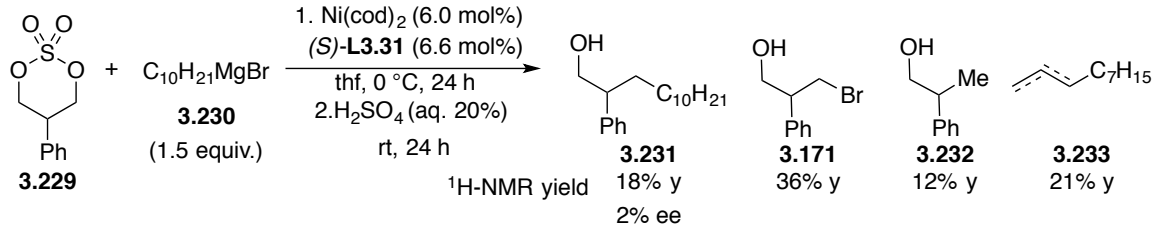
**Scheme 3.50: Synthesis of β-Chiral Alcohols via Asymmetric Hydrogenation[101d] and Diastereoselective Alkylation[102b]**




Our investigation into the use of aliphatic Grignard reagents began by subjecting phenyl substituted cyclic sulfate **3.229** to nickel-catalyzed cross-coupling with Grignard reagent **3.230**. Nickel-catalyzed desymmetrization of **3.229** with **3.230** resulted in a mixture of products, with desired **3.231** only isolated in 18% yield and 2% ee (Scheme 3.35).

[102] For selected examples see: (a) Bello, J. E.; Millar, J. G. *Tetrahedron: Asymm.* **2013**, *24,* 822. (b) Cao, J.; Perimutter, P. *Org. Lett.* **2013**, *15*, 4327. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361. (c) Myers, A. G.; Yang, B. J.; Chen. H.; McKinstry, L.; Kopecky, D. G.; Gleason, J. L. *J. Am. Chem. Soc.* **1997,** *119*, 6496.

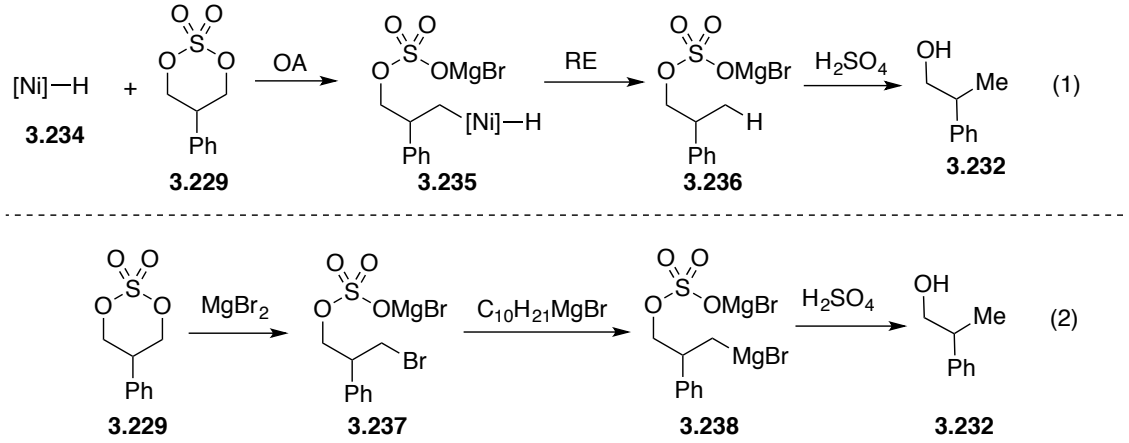
**Scheme 3.51: Initial Results in Desymmetrization with Alkyl Nucleophiles**




The byproducts of the reaction included **3.233**, which is presumably formed by β-hydride elimination after transmetalation of the Grignard reagent to nickel. Undesired alcohol **3.232** could be formed through one of two pathways. Since β-hydride elimination appeared to occur, the Ni-hydride formed could oxidatively add to the cyclic sulfate; subsequent reductive elimination would yield the reduced cyclic sulfate **3.236** and **3.232** upon acid hydrolysis (Scheme 3.52, eq. 1). Related to this, the palladium-catalyzed reduction of alkyl electrophiles with EtMgBr as a hydride source has been previously developed and is proposed to occur via the pathway describe in Scheme 3.52, eq. 1.[103] The other proposed pathway to obtain reduced product **3.232** involves initial ring-opening of cyclic sulfate **3.229** to form alkyl bromide **3.237** (Scheme 3.52, eq. 2). Intermolecular magnesium exchange between alkyl bromide **3.237** and Grignard reagent **3.230** then occurs, followed by protonation upon work up.[103b]

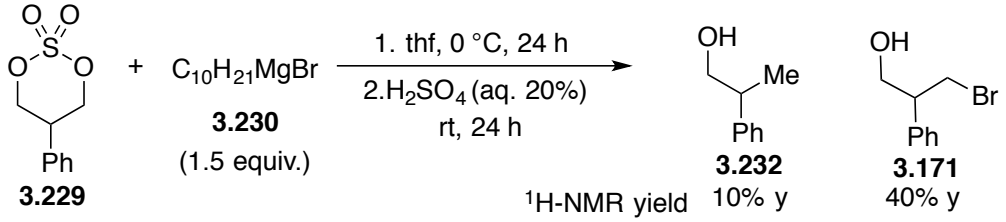
[103] (a) Castle, P. L.; Widdowson, D. A. *Tetrahedron Lett.* **1989**, *30*, 4779. (b) Milczek, E. L.; Palmiero, L.; Sewell, S. L.; Knight, K. S. *Transition Met. Chem.* **2006**, *31*, 27.

**Scheme 3.52: Proposed Pathways for the Formation of 3.232**




To differentiate between these two mechanisms, a reaction was performed without nickel catalyst. Due to the formation of **3.232** without a nickel catalyst (Scheme 3.53), it likely formed exclusively *via* magnesium bromide exchange (Scheme 3.52, eq. 2). This product is likely not observed with aryl Grignard reagents because the equilibrium between primary carbanions (such as **3.230**) and $sp^2$ carbanions would lie toward the aryl nucleophile.

**Scheme 3.53: Formation of 3.232 in the Absence of Nickel Catalyst**




Unfortunately, significant efforts to suppress byproduct formation and increase enantioselectivity in the cross-coupling of alkyl Grignard reagents by changing solvent,

ligand, nickel-precatalyst, catalyst loading, or Grignard reagent counter ion (RMgCl) failed to give desired results. Attempts to use nucleophiles such as alkyl boranes and alkyl zinc halides also failed to give the desired cross-coupled product without significant byproduct formation. Perhaps gaining a better understanding of the reaction mechanism could lead to conditions that allow for cross-coupling of vinyl or alkyl nucleophiles.

### *3.5.8 Mechanistic Studies on Desymmetrization of Cyclic Sulfates*

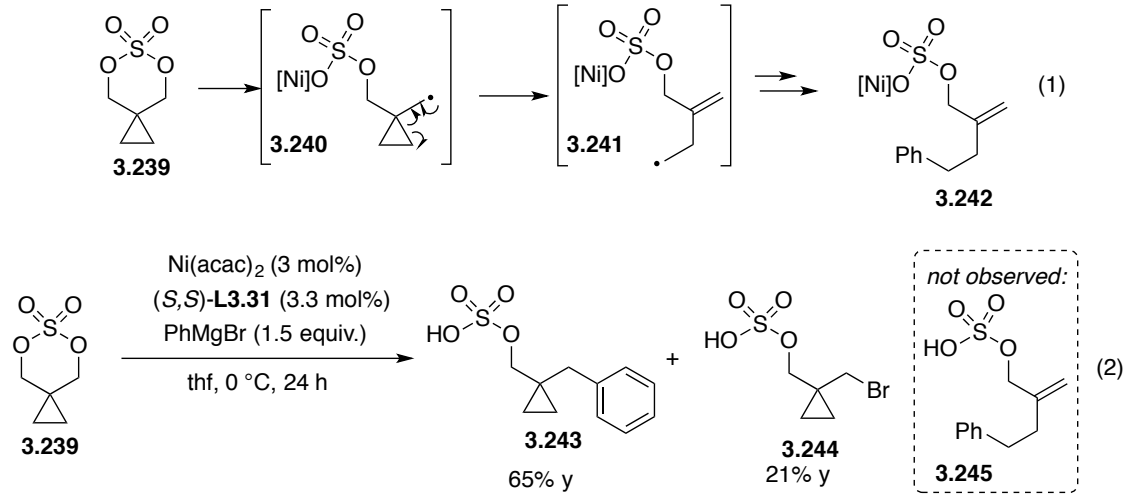
As mentioned in section 3.5.3, the proposed mechanism of the nickel-catalyzed Kumada coupling of cyclic sulfates proceeds through a Ni(0)/Ni(II) cycle, in which intermediate carbon-centered radicals do not appear to be present. However, several nickel-catalyzed cross-couplings of non-activated alkyl halides under very similar conditions have been determined to proceed through Ni(I)/Ni(III) cycles with radical intermediates.[104] To probe for radical intermediates, cyclic sulfate **3.239** was prepared and subjected to the nickel-catalyzed Kumada coupling with PhMgBr. If a carbon centered radical **3.240** were to form during the reaction, the cyclopropyl ring would likely rupture leading to **3.242** (Scheme 3.54, eq. 1).[105] Olefinic product **3.242**, arising from ring opening,

[104] (a) Vechorkin, O.; Proust, V.; Hu, X. L. *J. Am. Chem. Soc*., **2009**, *131*, 9756. (b) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340. (c) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004,** *126*, 7788. (d) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc* **2005**, *127*, 510. (e) Schley, N.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136,* 16588

[105] For examples of cyclopropyl electrophiles as radical probes in Ni-cat. cross-couplings see: (a) Phapale, V. B.; Buñ uel, E.; García-Iglesias, M.; Cardenas, D. J. *Angew. Chem., Int. Ed*. **2007**, *46*, 8790. (b) Vechorkin, O.; Csok, Z.; Scopelliti, R.; Hu, X. *Chem. - Eur. J.* **2009**,

was not observed but rather a mixture of sulfate half-esters **3.243** and **3.244** (Scheme 3.54, eq. 2). The brominated byproduct **3.244** is likely formed due to a slower-oxidative addition to the hindered C-O bond, allowing for the background ring-opening (*vide supra*). Ring opening of a substituted cyclopropylcarbinyl radical (**3.240**) has a rate of 8.6 x $10^7$ $s^{-1}$, so though the absence of **3.245** supports the absence of such a radical species, it is not definitive.[106]

**Scheme 3.54: Coupling Reaction Using Radical-Probe Substrate**




In 2007, Kambe and co-workers developed a copper-catalyzed cross-coupling of alkyl halides with aryl Grignard reagents.[107] To probe the stereochemistry of the reaction,

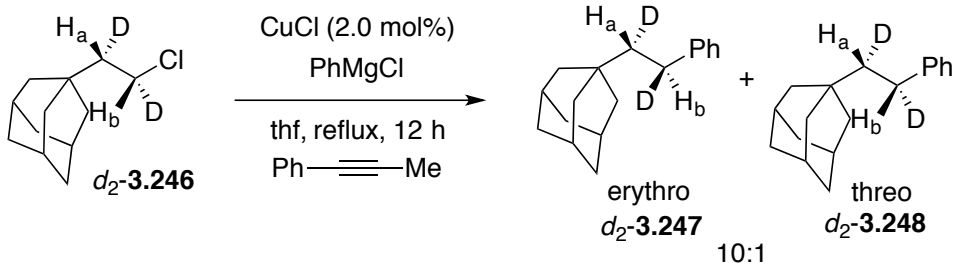
*15*, 3889. (c) Terao, J.; Watanabe, H.; Ikume, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222.

[106] Martin-Esker, A. A.; Johnson, C. C.; Horner, J. H.; Newcomb, M. *J. Am. Chem. Soc.* **1994**, *116*, 9174.

[107] Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 2086. For previous examples of similar mechanistic probe experiments see: (a) Bock, P. L.; Boschetto, D. J.; Rasmusen, J. R.; Dermers, J. P.; Whitesides, G. M. *J. Am. Chem.*

***d*$_2$-3.246** was synthesized and subjected to the cross-coupling (Scheme 3.55). The reaction proceeded with primarily inversion of stereochemistry at the reactive site to give ***d*$_2$-2.247**, which is consistent with an $S_N2$-type mechanism.

**Scheme 3.55: Stereochemical Probe in Cu-Catalyzed Cross-Coupling By Kambe**




We considered that a similar strategy could be applied to our system. Examination of cyclic sulfate ***d*-3.254** in cross-coupling could further reveal features of the proposed Ni(0)/Ni(II) mechanism.[108] If an $S_N2$-type mechanism is operative then inversion at the cross-coupling site should be observed. However, if a carbon-centered radical is formed during the reaction upon asymmetric homolysis of the C-O bond, then scrambling at the deuterium-labeled carbon may be observed.

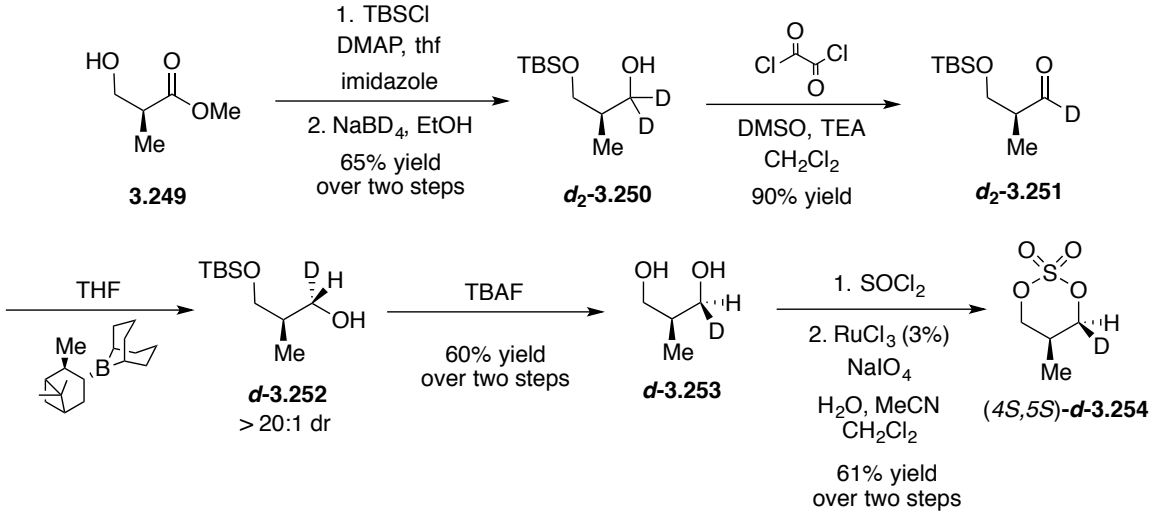
Cyclic sulfate ***d*-3.254** was synthesized in seven steps from commercially available (*S*)-Roche ester **3.249** (Scheme 3.56). Protection of Roche ester with TBSCl followed by sodium borodeuteride reduction yields monoprotected diol ***d*$_2$-3.250** in 65% yield. After

*Soc.* **1974**, *96*, 2814. (b) Jensen, K. L.; Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2014**, *136*, 11145.

[108] For similar labeling experiments in nickel-catalyzed cross-coupling reaction see: Jensen, K. L.; Standely, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2014**, *136*, 11145.

oxidation, Midland reduction of deuteroaldehyde ***d*-3.251** gives monoprotected diol ***d*-3.252** in > 20:1 dr.[109] The cyclic sulfate ***d*-3.254** is obtained after TBAF deprotection of ***d*-3.252** to diol ***d*-3.253** followed by cyclization and oxidation.

**Scheme 3.56: Synthesis of Stereochemical Probe *d*-3.254**

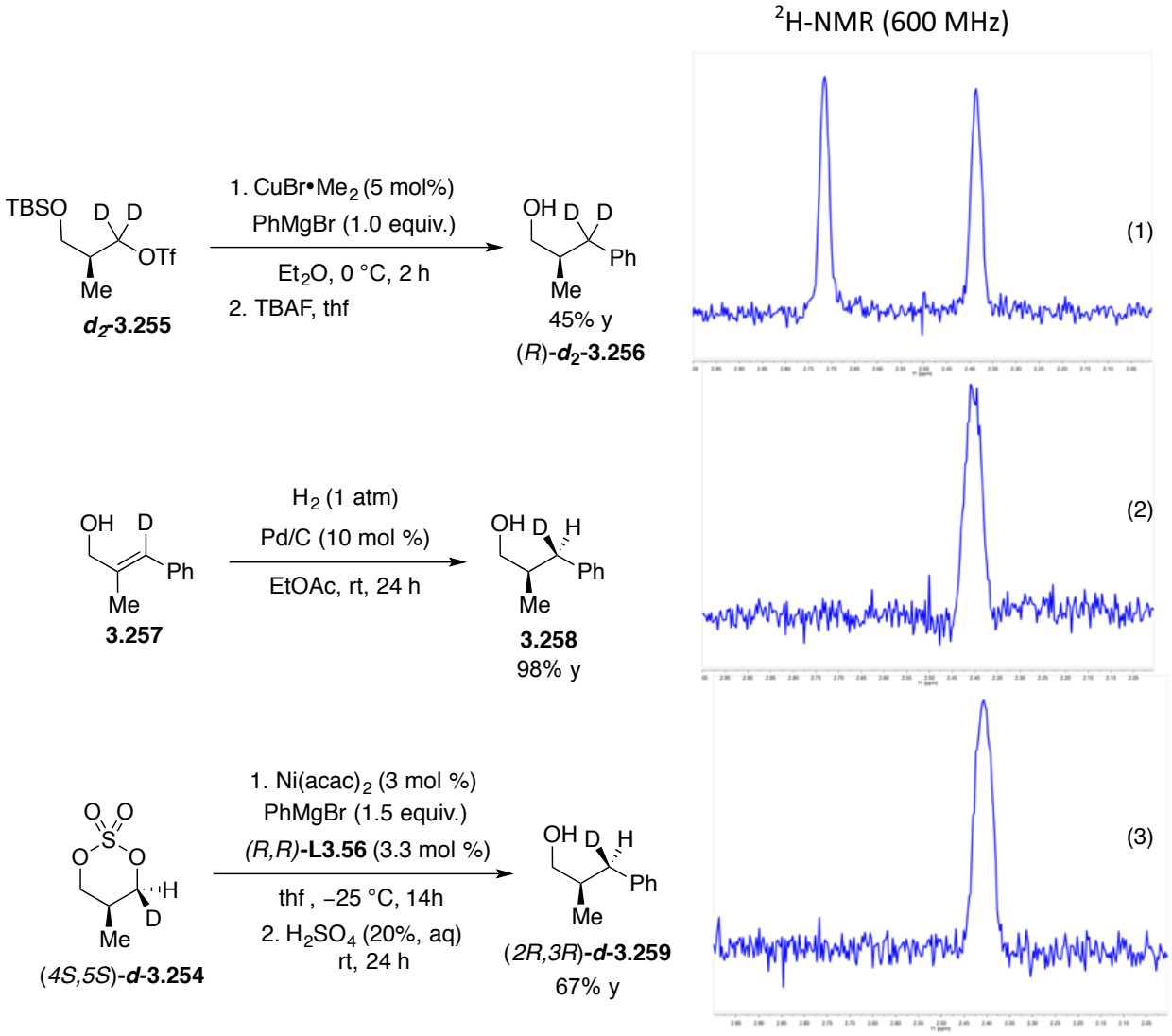



We predicted that deuterium NMR of the product mixture would be a simple method to determine the outcome of the cross-coupling of ***d*-3.254**. In order to use this method ***d*$_2$-3.256** was synthesized via copper-catalyzed cross-coupling (Scheme 3.57, eq. 1). A deuterium NMR of ***d*$_2$-3.256** was obtained for future comparison and showed two well resolved diastereotopic deuterium signals in the benzylic region. In addition to ***d*$_2$-3.256**, hydrogenation of ***d*-3.257** resulted in a racemic mixture of diastereometrically-enriched ***d*-3.258** (Scheme 3.57, eq. 2). This diastereomer of product would be the result

[109] For a review on the Midland Reduction see: Midland, M. M. **1989**, *89*, 1553. For ananlysis of stereochemical outcome of reduction see: Gerlach, H.; Zagalak, B. *J. Chem. Soc.; Chem. Comm.* **1973**, 274.

of an $S_N2$ type-oxidative addition of nickel to ***d*-3.254**, assuming that reductive elimination occurs with retention of configuration. With authentic products for comparison, Ni-catalyzed cross-coupling of ***d*-3.254** in the presence of (*R,R*)-**L3.56** was performed (Scheme 3.57, eq. 3). It was determined that the reaction of ***d*-3.254** furnished stereoisomer ***d*-3.259** with a high level of stereospecificity (90% ds). This result suggests that the reaction proceeds via an $S_N2$ type pathway with stereoinversion, and does not involve the intermediacy of carbon-based radicals.

**Scheme 3.57: Probing Stereochemical Outcome of the Asymmetric Ni-Catalyzed Kumada Coupling**




It is not surprising that the cross-coupling of cyclic sulfates would proceed in the absence of carbon centered radicals, as the bond dissociation energy of the C-O bond of methyl methanesulfonate (425.2 kJ/mol)[110] is significantly higher than that of the alkyl bromides typically used in Ni-catalyzed cross-couplings involving carbon-centered

[110] Ding, L.; Zheng, W.; Wang, X. *J. Phys. Chem. A.* **2015**, *119*, 3488.

radicals (C-Br = 276 kJ/mol). Though a Ni(I)/Ni(III) cycle involving radical species has been ruled out, there are a few experimental results that suggest the mechanism is not a typical Ni(0)/Ni(II) cycle with transmetalation occurring after oxidative addition. Specifically, though the brominated byproduct formation has been suppressed, the electronic nature of the Grignard reagent still influences the enantioselectivity of the reaction (Scheme 3.58, **3.81** and **3.181**). This result suggests that the involvement of the nucleophile in the reaction occurs prior to the stereochemistry determining step. This could also be a reason why *ortho*-substituted aromatic Grignard reagents do not participate readily in the cross-coupling: due to added steric hindrance at the metal center oxidative addition may be slow. Our revised mechanistic proposal involves a Ni(I)/Ni(III) cycle with transmetalation occurring prior to oxidative addition (Scheme 3.58). This type of Ni(I)/Ni(III) mechanism does not typically proceed without the intermediacy of a Ni(II) species, but has been previously proposed in cross-coupling reactions.[111] In this mechanism, the Ni(I) species **3.260** could be formed after transmetalation to a Ni(I)-X formed through a comproportionation of a Ni(0) and Ni(II) species.[112] We also propose that the cyclic sulfate reacts in the conformation in which the substituent is in the axial position (**3.141**). This proposal is because, one would predict that increasing the steric bulk adjacent to the reactive site of an $S_N2$-type reaction would lead to changes in rate and enantioselectivity.

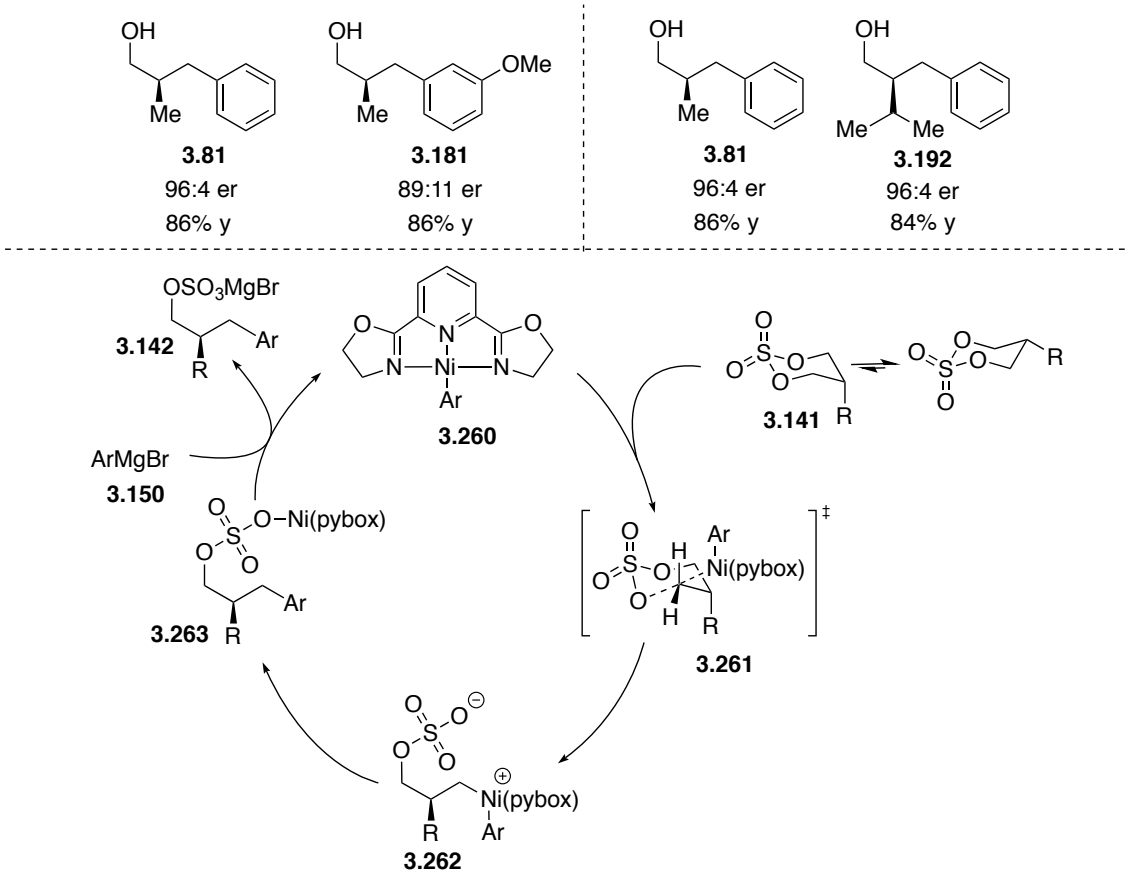
---

[111] (a) Meng, J. J.; Gao, M.; Wei, Y.-P.; Zhang, W.-Q. *Tetrahedron Lett.* **2014**, *55*, 2107. (b) Li, Z.; Jiang, Y. Y.; Fu, Y. *Chem. Eur. J.* **2012**, *18*, 4345. (b) Zhang, K.; Conda-Sheridan, M.; Cooke, S. R.; Louie, J. *Organometallics* **2011**, *30*, 2546,

[112] (a) Beromi, M. M.; Nova, A.; Balcells, D.; Brasacchio, A. M.; Brudvig, G. V.; Guard, L. M.; Hazari, N.; Vineyard, D. J. *J. Am. Chem. Soc.* **2016**, JUST ACCEPTED. (b) Saraev, V. V.; Kraikivskii, P. B.; Matveev, D. A.; Kuzakov, A.; Vil'ms, A. I.; Fendonia, A. A. *Russ. J. Coord. Chem.* **2008**, *34*, 438.

This is not the case in the asymmetric Kumada coupling developed as *i*-Pr and methyl substituted cyclic sulfates give the same enantioselectivities and yields (Scheme 3.58, **3.81** vs **3.192**).

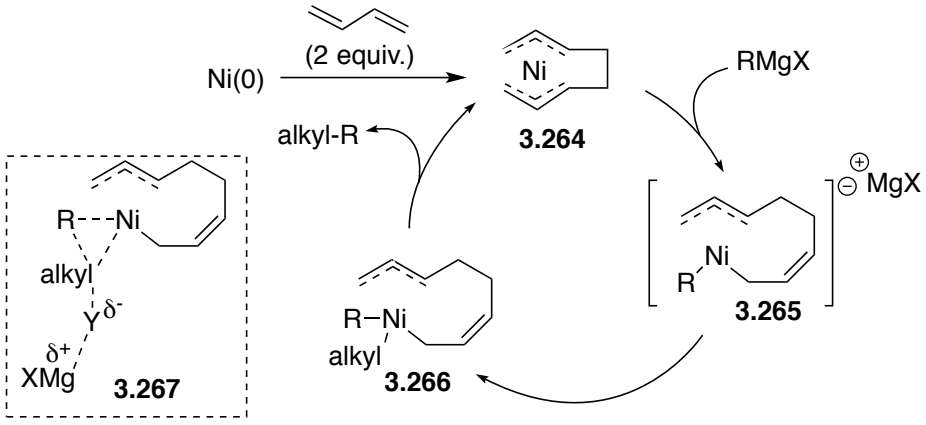
**Scheme 3.58: Proposed Ni(I)/Ni(III) Mechanism in Ni-Catalyzed Kumada Coupling**




Though the mechanism above is plausible, there is little experimental evidence to favor this mechanism over other mechanistic possibilities outside of the Ni(I)/Ni(II)/Ni(III) pathway. Kambe and co-workers propose a very unique Ni(II)/Ni(IV) cycle for their Ni-catalyzed Kumada couplings of alkyl halide and tosylates with butadiene additives

(Scheme 3.59).[113] The authors propose bis(allyl)Ni(II) **3.264** species as a catalytic intermediate formed from oxidative cyclization of two butadiene molecules to a Ni(0) species. Transmetalation of the Grignard reagent to the Ni(II) yields anionic nickelate species **3.265**. The high electron density of **3.265** allows it to be a very active catalyst for the oxidative addition to unactivated alkyl electrophiles. After oxidative addition, which is proposed to also be assisted by Lewis acid activation of the electrophile (**3.267**), reductive elimination releases the product and reforms **3.264**.

**Scheme 3.59: Ni(II)/Ni(IV) Kumada Coupling of Alkly Electrophiles by Kambe**

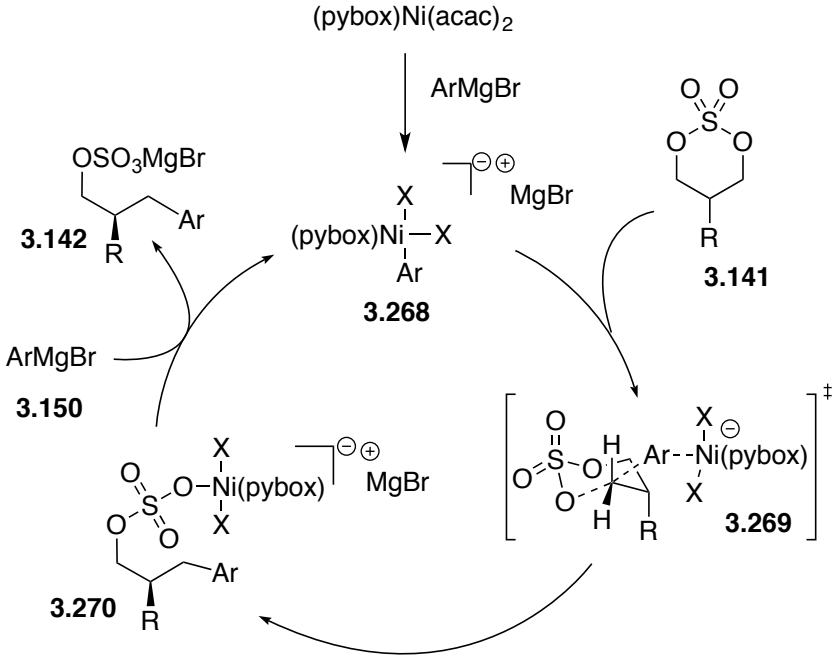



The above Ni(II)/Ni(IV) mechanism cannot be directly applied to the desymmetrization of cyclic sulfates because we have not added dienes, but perhaps a

[113] (a) Terao, J.; Kambe, N. *Angew. Chem. Int. Ed.* **2004**, 43, 6180. (b) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222.

nickelate species is the active nickel complex in the desymmetrization (Scheme 3.60).[114] In this case a traditional oxidative addition/reductive elimination would not occur but rather nucleophilic transfer of the aryl ring to open the cyclic sulfate, similar to $S_N2$ reactions of organocuprates.[115] This mechanism is still consistent with inversion occurring at the electrophilic carbon, as well as the impact the electronic and steric nature of the Grignard reaction have on the reaction outcome.

**Scheme 3.60: Desymmetrization of Cyclic Sulfates via Nickelate Formation**

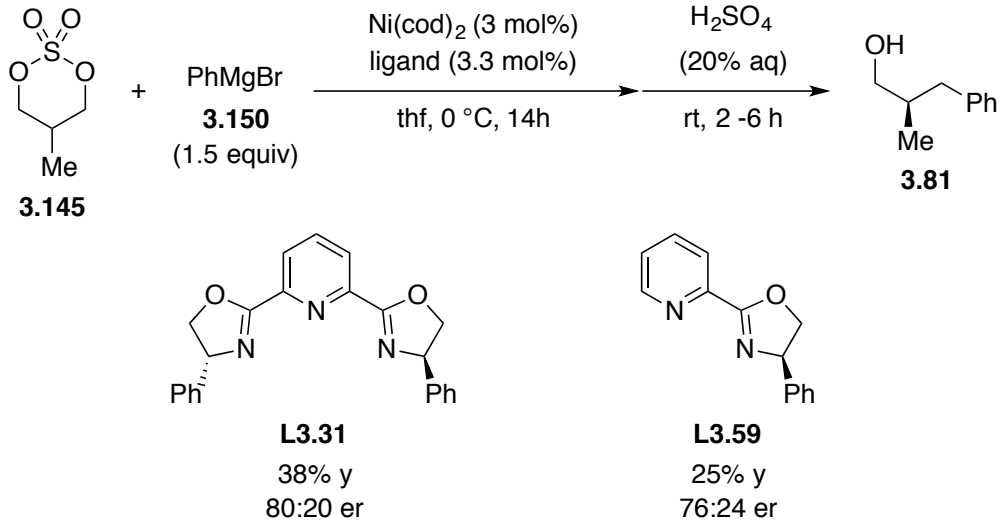



[114] This type of metalate mechanism has also been proposed in iron-catalyzed Kumada couplings: Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949.

[115] (a) Nakamura, E.; Mori, S. *J. Am. Chem. Soc.* **1998**, *120*, 8273. (b) Corey, E. J.; Posner, G. H. J. Am. Chem. Soc. 1967, 89, 3911. (b) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783. (c) Guo, C.-Y.; Brownawell, M. L.; San Filippo, J., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 6028. (d) Pearson, R. G.; Gregory, C. D. J. *Am. Chem. Soc.* **1976**, *98*, 4098.

The above mechanism would require nickel to be six-coordinate with the chiral ligand scaffold and though six-coordinate nickel(II) complexes are not often described, they are known in the literature and have been isolated and characterized with porphyrin ligands.[116] However, experimental evidence indicates that perhaps the ligand is only binding in a bidentate fashion, resulting in what would be a 5-coordinate nickel species above. Although tricoordinate PyBox ligand **L3.56** was used for the scope of the cross-coupling, later it was found that asymmetric Kumada coupling of **3.145** in the presence of monooxazoline **L3.59** occurs with similar levels of enantioselectivity as PyBox **L3.56** (Scheme 3.61).

**Scheme 3.61: Comparison of PyBox and PyOx Ligands in Asymmetric Kumada Coupling**




[116] (a) Kirner, J. F.; Garofalo, J. Jr.. Scheidt. *Inorg. Nuc. Chem. Lett*. **1975**, *11*, 107. (b) Jia, W. G.; Li, D.-D.; Yan, L.-Q.; Sheng, E. H.; Dai, Y. C. *J. Coord. Chem.* **2014**, *67*, 363. (c) Wang, Y.-Y.; Lin, S.-A.; Zhu, F. M.; Gao, H.-Y.; Quing, W. *Inorg. Chim. Acta* **2009**, 362, 166.

## 3.6 Conclusions

A novel Ni-catalyzed asymmetric Kumada coupling of prochiral cyclic sulfates has been presented. The cross-coupling in the presence of **L3.56** proceeds smoothly to give enantioenriched β-chiral alcohols in high yield and selectivity for a number of cross-coupling partners. We have also demonstrated that the desymmetrization is effective in the synthesis of both carbon and oxygenated stereocenters. However, due to the harsh conditions necessary for the synthesis of cyclic sulfates, the scope of the electrophile is limited to those without oxidant sensitive functional groups. Unfortunately, efforts to expand the scope to include alkyl nucleophile coupling partners failed due to byproducts derived from bromination and reduction of the cyclic sulfate. Mechanistic probes have revealed that this reaction likely proceeds by an $S_N2$ oxidative addition without orgnoradical intermediates. To determine the complete mechanism, additional experimental evidence must be gathered in order to discern between possible pathways: Ni(I)/Ni(III), Ni(0)/Ni(II), or Ni(II).

This method represents one of the only reported Ni-catalyzed asymmetric cross-couplings of alkyl electrophiles which is proposed to not proceed *via* radical intermediates. Ideally, with future efforts in development of a desymmetrization with non-Grignard reagent nucleophiles and efforts into the development of mild methods for the synthesis of cyclic sulfates, the full scope and utility of this method can be demonstrated.

## 3.7 Experimental

### *3.7.1 General Information*

$^{1}$H-NMR spectra were recorded on a Varian Gemini-500 (500 MHz), Varian Inova 500 (500 MHz) or Varian Gemini-600 (600 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm, $CD_3OD$: 3.31 ppm). Data are reported as the following: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent), and coupling constants (Hz). Coupling constants are reported to the nearest 0.5 Hz. $^{2}$H-NMR spectra were recorded on a Varian Gemini-600 (92 MHz) spectrometer. 13C NMR spectra were recorded on a Varian Gemini-500 (125 MHz) or Varian Gemini-600 (151 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.0 ppm, $CD_3OD$: 49.2 ppm). Infrared (IR) spectra were recorded on a Burker alpha spectrophotometer, $\nu_{max}$ $cm^{-1}$. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High-resolution mass spectrometry (DART-TOF) was performed at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel ($SiO_2$, 230×450 Mesh) purchased from Silicycle. Thin Layer

Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate ($KMnO_4$) in water, or phosphomolybdic acid (PMA) in ethanol. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector.

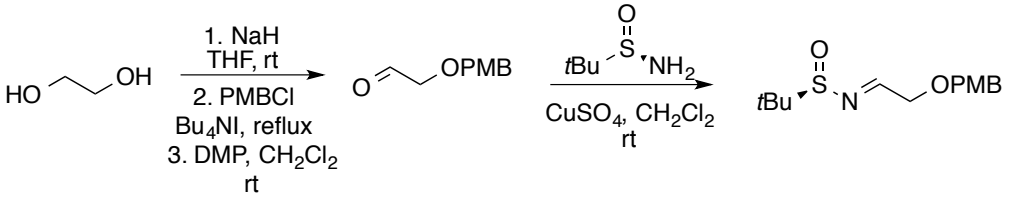
All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon, unless otherwise stated. Tetrahydrofuran (THF), toluene, diethyl ether ($Et_2O$) and dichloromethane (DCM) were purified using a Pure Solv MD-4 solvent purification system from Inert (previously; Innovative Technology Inc.) by passing through two activated alumina columns after being purged with argon. Thionyl chloride was purchased from Alfa, sodium(meta)periodate, 2-methyl-1,3-propanediol, pyridine-2,6-carbonitrile, Montmorillonite K 10, and *(S)*-Roche ester were purchased from Aldrich. Other 1,3-diols were obtained after reduction of the corresponding malonate with $LiAlH_4$.[117] Ruthenium(III) chloride hydrate, *(S)*-(-)-2-methyl-2-propanesulfinamide, and *(R)*-(+)- 2-methyl-2-propanesulfinamide were purchased from Combi-Blocks. Nickel(II) acetylacetonate and methanol (99.9%, extra dry), and hydrochloric acid (4 N in 1,4-dioxane) were purchased from Acros Organics. Bis(1,5-cyclooctadiene)nickel(0) was purchased from Strem Chemicals, Inc. Dess-Martin

[117] Zimmerman, N.; Pinard, P.; Carboni, B.; Gosselin, P., Caulon-Nourry, C.; Dujardin, G.; Collet, S.; Lebreton, J. *Eur. J. Org. Chem.* **2013**, *2013,* 2303

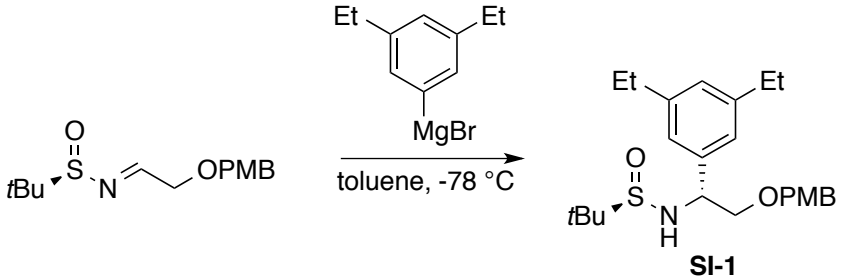
periodinane and 1-bromo-3,5-diethylbenzene were purchased from Oakwood Chemicals. Sodium borodeuteride was purchased from Cambridge Isotope Laboratories. Copper(II) sulfate was purchased from Fisher and dried by heating before use. All other chemicals were purchased from Fisher or Aldrich and used without further purification.

### *3.7.2 Experimental Procedures*

#### *3.7.2.1 Ligand Synthesis*



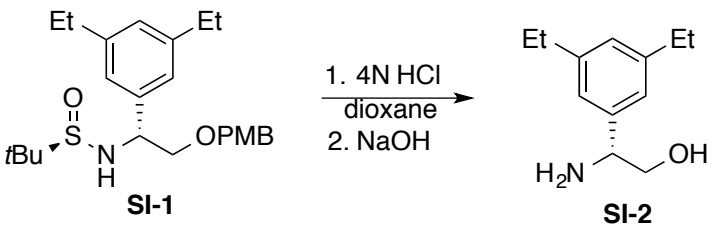

***(R,E)-N-(2-((4-methoxybenzyl)oxy)ethylidene)-2-methylpropane-2-sulfinamide*** was prepared according to the literature procedure from ethylene glycol as shown above.[118]



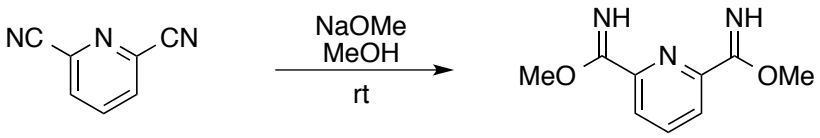

**SI-1**

[118] Crimmins, M. T.; Shamszad, M. *Org. Lett.,* **2007**, *9*, 149

***(R)*-N-((*R*)-1-(3,5-diethylphenyl)-2-((4-methoxybenzyl)oxy)ethyl)-2-methylpropane-2-sulfinamide (SI-1):** Prepared according to the literature procedure with slight modification.[1] To a solution of imine (3.79 g, 13.4 mmol) in toluene (0.2 M) at -78 °C was added aryl magnesium bromide (1.75 equiv). Aryl magnesium bromide was prepared from Mg turnings (733 mg, 30.6 mmol), 1-bromo-3,5-diethylbenzene (4.0 mL, 23.5 mmol) and 12 mL of dry diethyl ether. The mixture was stirred for 2 h at −78 °C after which the reaction was quenched with saturated ammonium chloride. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (10:1 hexane: ethyl acetate to 1:1 hexane: ethyl acetate) to provide a single diastereomer of the product as a yellow oil (5.30 g, 95% yield). $R_f$ = 0.17 (4:1 ethyl acetate: hexane, stain in $KMnO_4$ ).$^1$H NMR (600 MHz, $CDCl_3$): δ 1.19 -1.22 (15H, m), 2.57 -2.63 (4H, m), 3.53 (1H, t, *J* = 10.2 Hz), 3.59 -3.61 (1H, m), 4.15 (3H, s), 4.50 (2H, ABq, $J_{AB}$ = 11.4 Hz, $\Delta\nu_{AB}$ = 67.2 Hz), 6.86 (2H, d, *J* = 9.0 Hz), 6.95 -6.97 (3H, m), 7.26 (2H, d, *J* = 9.0 Hz) ; $^{13}$C NMR (151 MHz, $CDCl_3$): δ 15.4, 22.6, 28.7, 55.3, 55.4, 57.2, 72.2, 73.9, 113.8, 124.8, 127.3, 129.5, 129.8, 138.5, 114.3, 159.3; IR (neat): 2961 (m), 2930 (m), 2867 (m), 1586 (m), 1459 (w), 1247 (m), 1072 (s), 1035 (w), 711 (m) $cm^{-1}$; HRMS-(DART-TOF) for $C_{24}H_{36}N_1O_3S_1$ [M+H]: calculated: 418.24159, found: 418.24317.



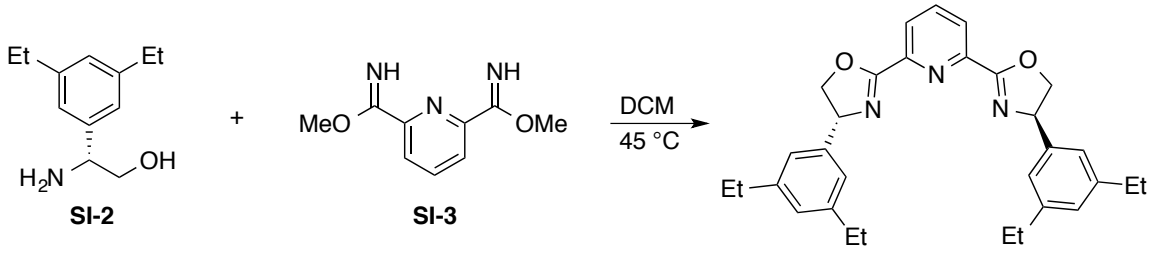

**(*R*)-2-Amino-2-(3,5-diethylphenyl)ethan-1-ol (SI-2):** To an oven dried 100 mL round bottom flask with stir bar containing a solution of **SI-1** (5.30 g, 12.7 mmol) in methanol (25 mL) under nitrogen was added 4M HCl in 1,4-dioxane (31.75 mL, 127 mL) dropwise. The reaction was allowed to stir overnight before solvent removed under reduced pressure. The crude solid was suspended in ethyl acetate (100 mL) and 4M NaOH (120 mL) added while solution stirred vigorously. Solution was allowed to continue stirring for 20 min before organic layer separated and aqueous layer extracted with ethyl acetate (5 x 15 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (20:1 $CH_2Cl_2$: MeOH) to provide the desired product as a light yellow solid (1.50 g, 61% yield). $R_f$ = 0.09 (10:1 $CH_2Cl_2$: MeOH, stain in $KMnO_4$). $^1$H NMR (600 MHz, $CDCl_3$): δ 1.23 (6H, t, *J* = 7.5 Hz), 1.99 (3H, s), 2.62 (4H, q, *J* = 7.5 Hz), 3.54 (1H, dd, *J* = 10.5 Hz, 8.5 Hz), 3.73 (1H, dd, *J* = 10.5 Hz, 4.5 Hz), 3.99 (1H, dd, *J* = 8.0 Hz, 4.5 Hz), 6.97 (3H, s); $^{13}$C NMR (151 MHz, $CDCl_3$): δ 15.6, 28.8, 57.4, 68.0, 123.3, 126.7, 142.7, 144.7; IR (neat): 3278 (br, m), 3015 (m), 2963 (m), 2930 (m), 2872 (m), 1602 (m), 1512 (m), 1047 (m), 869 (m) $cm^{-1}$; HRMS-(DART-TOF) for $C_{12}H_{20}NO$[M+H]: calculated: 194.15449, found: 194.15476. $[\alpha]^{22}_D$ = -30.670 (*c* = 0.725, $CDCl_3$).




**SI-3**

**Dimethyl pyridine-2,6-bis(carbimidate) (SI-3):** Prepared according to the literature procedure with slight modification.[119] To an oven dried 50 mL round bottom flask equipped with magnetic stir bar in a dry box under an argon atmosphere was added sodium methoxide (52 mg, 0.97 mmol). The reaction flask was sealed with septa, removed from the dry box and placed under $N_2$ before methanol (20 mL) added. Reaction was cooled to 0 °C and pyridine-2,6-dicarbonitrile (1.25 g, 9.67 mmol) added as a solid. The resulting reaction mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched by the addition of acetic acid (0.12 mL) at 0 °C and resulting solution was concentrated by rotary evaporation, resulting in a white solid (1.38 g, 72% yield) which was carried forward without purification. $^{1}$H NMR (500 MHz, $CDCl_3$): δ 4.04 (6H, s), 7.93 (3H, s), 9.24 (2H, s); $^{13}$C NMR (151 MHz, $CDCl_3$): δ 54.0, 122.6, 138.9, 146.9, 165.9; IR (neat): 3286 (w), 3270 (w), 2957 (w), 1652 (s), 1571 (m), 1338 (s), 1083 (s), 943 (w) $cm^{-1}$; HRMS-(DART-TOF) for $C_9H_{12}N_3O_2$ [M+H]: calculated: 194.09295, found: 194.09211.

[119] Jones, B. A.; Bradshaw, J. S.; Brown, P. R.; Christensen, J. J.; Izatt, R. M. *J. Org. Chem.* **1983**, *48*, 2635

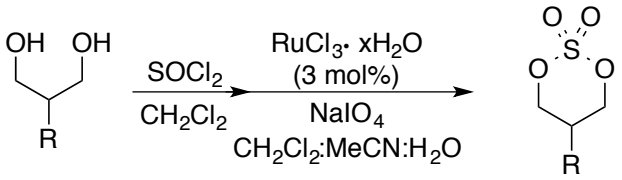



**2,6-Bis((*R*)-4-(3,5-diethylphenyl)-4,5-dihydrooxazol-2-yl)pyridine ((R,R)-L56):**

Prepared according to the literature procedure with slight modification.[120] To an oven dried 15 mL pressure vessel with stir bar in dry box was added **SI-2** (125 mg, 0.65 mmol), amino alcohol **SI-3** (249 mg, 1.29 mmol) and dichloromethane (2.2 mL). The reaction vessel was sealed, removed from dry box and allowed to stir at 45 °C for 48 h. The reaction was then allowed to cool to room temperature and washed with water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation. The crude product was purified by silica gel chromatography (20:1 $CH_2Cl_2$: MeOH) to provide the desired product as a viscous yellow oil (203 mg, 65% yield). $R_f$ = 0.24 (20:1 $CH_2Cl_2$: MeOH, stain in PMA). $^1$H NMR (600 MHz, $CDCl_3$): δ 1.22 (12H, t, *J* = 7.8 Hz), 2.61 (8H, q, *J* = 7.8 Hz), 4.45 (2H, t, *J* = 9.0 Hz), 4.91 (2H, dd, *J* = 10.8 Hz, 9.0 Hz), 5.40 (2H, dd, *J* = 10.2 Hz, 9.0 Hz), 6.97 (6H, s), 7.91 (1H, t, *J* = 7.2 Hz), 8.36 (2H, d, *J* = 8.4 Hz); $^{13}$C NMR (151 MHz, $CDCl_3$): δ 15.6, 28.8, 70.5, 75.2, 123.8, 126.3, 127.0, 137.4, 141.6, 144.9, 146.8, 163.2; HRMS-(DART-TOF) for $C_{31}H_{36}N_3O_2$ [M+H]: calculated: 482.28075, found: 482.28240. $[\alpha]^{22}_D$ = 186.02 (*c* = 0.470, $CHCl_3$).

[120] Tse, M. K.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H.; Döbler, C.; Spannenberg, A.; Mägerlein, W.; Hugl, H.; Beller, M. *Chem, Eur. J.,* **2006**, *12*, 1855

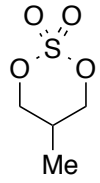
### *3.7.2.2 Preparation of Electropihles*



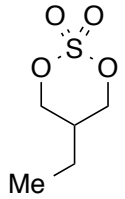

*General procedure for cyclic sulfate preparation:*

To a round bottom flask equipped with a stir bar, open to air, was added diol followed by dichloromethane ([substrate]= 1.5M). The solution was cooled to 0 °C and thionyl chloride (1.5 equiv.) added dropwise. The reaction was allowed to stir until determined complete by TLC (approximately 2 hours). The reaction mixture was then added dropwise to cold water, the organic layer was separated and washed with saturated sodium bicarbonate solution followed by water. The organic layer was then dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation. The crude product was then dissolved in $CH_2Cl_2$ (0.5M), MeCN, and water (1:1:2) and cooled to 0 °C. To this solution was added ruthenium chloride hydrate (3 mol%) and sodium periodate (1.5 equiv.) in portions. The solution was then allowed to warm to room temperature and stir until complete by TLC (approximately 1 hour). Once complete reaction diluted with diethyl ether and the organic layer was washed with the following: water (x 2), saturated sodium

bicarbonate, and saturated sodium chloride solution. The organic layer was then dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation. The crude reaction product was purified by silica gel chromatography or crystallization.

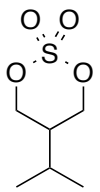


**5-Methyl-1,3,2-dioxathiane 2,2-dioxide.** Prepared according to the general procedure using 2-methyl-1,3-propanediol (2.7 mL, 30.0 mmol). The crude material was purified by recrystallization by dissolving in ethyl acetate and layering with hexanes to afford the title compound as white solid (3.20 g, 69% yield). $R_f$ = 0.33 (3:1 pentane: diethyl ether, stain in $KMnO_4$). $^1$H NMR (500 MHz, $CDCl_3$): δ 1.05 (3H, d, *J* = 7.0 Hz), 2.44 (1H, m), 4.44 (2H, dd, *J* = 11.5 Hz, 9.5 Hz), 4.58 (2H, dd, *J* = 11.5 Hz, 4.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 11.3, 28.1, 77.6; IR (neat) 2975 (w), 1460 (m), 1400 (s), 1386 (s), 1194 (s), 983 (m), 954 (m), 820 (m), 776 (m), 532 (m) $cm^{-1}$; HRMS-(DART-TOF) for $C_4H_9O_4S$ [M+H]: calculated: 153.02215, found: 153.02190.

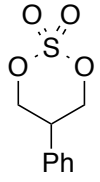


**5-Ethyl-1,3,2-dioxathiane 2,2-dioxide.** Prepared according to the general procedure using 2-ethyl-1,3-propanediol (1.88 g, 18.0 mmol). The crude material was purified by silica gel chromatography (1:1 pentane: diethyl ether to 100% diethyl ether) to afford the title compound as a clear, colorless oil (1.48 g, 49% yield). $R_f$ = 0.33 (3:1 pentane: diethyl ether, stain in $KMnO_4$). $^1$H NMR (600 MHz, $CDCl_3$): δ 1.01 (3H, t, *J* = 7.5 Hz), 1.47 (2H, tt, *J* = 7.5 Hz), 2.17 (1H, ddtd, *J* = 11.6 Hz, 8.7 Hz, 4.4 Hz, 3.0 Hz), 4.47 -4.50 (2H, m), 4.64 (2H, dd, *J* = 12.0 Hz, 4.2 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ

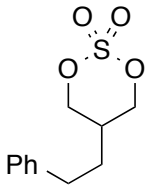
11.1, 19.8, 34.5, 76.5; IR (neat): 2970 (m), 2941 (m), 2882 (w), 1397 (s), 1194 (s), 968 (s), 875 (s), 773 (m) $cm^{-1}$; HRMS-(DART-TOF) for $C_5H_{11}O_4S_1$ [M+H]: calculated: 167.03780, found: 167.03761.



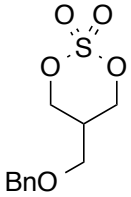
**5-Isopropyl-1,3,2-dioxathiane 2,2-dioxide.** Prepared according to the literature procedure using 2-isopropylpropane-1,3-diol (700 mg, 5.93 mmol). The crude material was purified by recrystallized in $Et_2O$/pentane at 2-8 °C, affording the title compound a white solid (758 mg, 71% yield). $^1H$ NMR (500 MHz, $CDCl_3$): δ 1.01 (6H, d, *J* = 7.0 Hz), 1.75 (1H, dq, *J* = 13.5 Hz, 7.0 Hz), 2.00 -2.08 (1H, m), 4.59 -4.64 (4H, m); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 20.1, 25.9, 38.9, 75.7; IR (neat): 2971 (m), 2878 (w), 1380 (s), 1196 (s), 976 (s), 835 (m), 535 (m) $cm^{-1}$; HRMS-(DART-TOF) for $C_6H_{13}O_4S_1$ [M+H]: calculated: 181.05345, found: 181.05330.



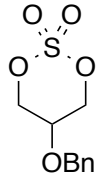
**5-Phenyl-1,3,2-dioxathiane 2,2-dioxide.** Prepared according to the general procedure using 2-phenylpropane-1,3-diol (1.0 g, 7.0 mmol). The crude material was purified by recrystallized from $Et_2O$ at 2-8 °C, affording the title compound a white solid (1.25 g, 83% yield). $^1H$ NMR (500 MHz, $CDCl_3$): δ 3.61 (1H, ddd, *J* = 15.5 Hz, 10.5 Hz, 5.0 Hz), 4.65– 4.69 (2H, m), 4.90- 4.94 (2H, m), 7.27- 7.28 (2H, m), 7.37- 7.42 (3H, m); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 39.4, 76.4, 127.9, 128.9, 129.5, 132.5; IR (neat): 3037(m), 2973 (w), 1496 (m), 1396 (s), 1193 (s), 1073 (m), 970 (s), $cm^{-1}$; HRMS-(DART-TOF) for $C_9H_{11}O_4S$ [M+H]: calculated: 215.03780, found: 215.03837.



**5-Phenethyl-1,3,2-dioxathiane 2,2-dioxide.** Prepared according to the general procedure using 2-phenethylpropane-1,3-diol (761 mg, 4.2 mmol). The crude material was purified by silica gel chromatography (4:1 hexane: ethyl acetate) to afford the title compound as a white solid (385 mg, 38% yield). $R_f$ = 0.47 (4:1 hexane: ethyl acetate, stain in $KMnO_4$). $^1$H NMR (600 MHz, $CDCl_3$): δ 1.76 (2H, q, *J* = 7.8 Hz), 2.24 (1H, ddq, *J* = 11.4 Hz, 7.8 Hz, 4.2 Hz), 4.49 (1H, dd, *J* = 11.5 Hz, 8.4 Hz), 4.62 (1H, dd, *J* = 11.5 Hz, 4.2 Hz), 7.16 (2H, d, *J* = 7.2 Hz), 7.24 (1H, t, *J* = 7.2 Hz), 7.33 (2H, t, *J* = 7.2 Hz); $^{13}$C NMR (151 MHz, $CDCl_3$): δ 28.1, 32.3, 32.7, 76.4, 126.7, 128.1, 128.8, 139.9; IR (neat): 2926 (w), 1398 (m), 1196 (m), 915 (m), 847 (m), 779 (m) cm$^{-1}$; HRMS-(DART-TOF) for $C_{11}H_{18}N_1O_4S_1$ [M+$NH_4$]: calculated: 260.09565, found: 260.09609.



**5-((Benzyloxy)methyl)-1,3,2-dioxathiane 2,2-dioxide**. Prepared according to the general procedure from 2-((benzyloxy)methyl)propane-1,3-diol (778 mg, 4.0 mmol). The crude material was purified by silica gel chromatography (1:1 $CH_2Cl_2$: pentane to $CH_2Cl_2$) to afford the title compound as a white solid (568 mg, 56% yield). $R_f$ = 0.31 (1:1 $CH_2Cl_2$: pentane, stain in $KMnO_4$). $^1$H NMR (500 MHz, $CDCl_3$): δ 2.37 (1H, m), 3.61 (2H, d, *J* = 7.0 Hz), 4.54 (2H, s), 4.66 (2H, dd, *J* = 13.2 Hz, 7.2 Hz), 4.77 (2H, dd, *J* = 14.4 Hz, 4.8 Hz);$^{13}$C NMR (125 MHz, $CDCl_3$): δ 33.8, 65.9, 73.6, 74.2, 127.7, 128.1, 128.6, 137.2; IR (neat): 2866 (m), 1454 (m), 1228 (s), 878 (m), 738 (m) cm$^{-1}$; HRMS-(DART-TOF) for $C_{11}H_{18}N_1O_5S_1$[M+$NH_4$]: calculated: 276.09057, found: 276.08985.



**5-(Benzyloxy)-1,3,2-dioxathiane 2,2-dioxide.** Prepared according to the literature procedure.[121] Spectral data is in accord with the literature reference.

### *3.7.2.3 Preparation of Aryl Grignard Reagents*

*Preparation of Aryl Grignard Reagents*

To an oven dried 2-neck round bottom flask with stir bar was added freshly ground magnesium turnings (360 mg, 15.0 mmol). The flask was fitted with a reflux condenser and put under nitrogen before a catalytic amount of $I_2$ and THF (10mL) added, the solution was allowed to stir for 30 min to activate the magnesium. Once activated, aryl bromide (10.0 mmol) was added dropwise, the mixture was then allowed to reflux for 2 h. The freshly prepared Grignard reagent was transferred by cannula to a round bottom flask and allowed to sit at 2-8 °C overnight before use. Aryl Grignard reagents were titrated according to method developed by Knochel.[122]

*Preparation of (1-methyl-1H-indol-5-yl)magnesium bromide:*

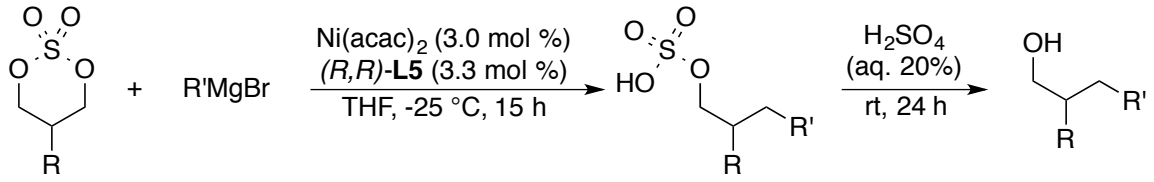
To an oven dried 2-neck round bottom flask with stir bar was added freshly ground magnesium turnings (720 mg, 30.0 mmol). The flask was fitted with a reflux condenser, put under nitrogen, and THF (5 mL) added. To this was added 1,2-dibromoethane (64 µL,

[121] Muraoka, O.; Yoshiaki, K.; Takahashi, H.; Minematsu, T.; Lu, G.; Tanabe, G.; Wang, T.; Matsuda, H.; Yoshikawa, M. *Bioorg. Med. Chem.,* **2006**, *14*, 500

[122] Krasovskiy, A.; Knochel, P. *Synthesis*, **2006**, *5*, 890

0.75 mmol) and 5-bromo-1-methyl-1*H*-indole (209mg, 1.0 mmol) and allowed to stir at 52 °C to activate the magnesium. Once activated, remaining aryl bromide (2.92 g, 14.0 mmol) in THF (10.0 mL) was added dropwise, the mixture was then allowed to stir at 52 °C for 2 h. The freshly prepared Grignard reagent was transferred by cannula to a round bottom flask and allowed to sit at 2-8 °C overnight before use. (1-methyl-1*H*-indol-5-yl)magnesium bromide was titrated according to method developed by Knochel.[6]

### *3.7.2.4 Experimental Procedure for Enantioselective Kumada Coupling*




*General cross-coupling procedure A (Dry-box)*:

An oven dried 2-dram vial equipped with a magnetic sir bar in dry box under an argon atmosphere was charged successively with 2,6-bis((*R*)-4-(3,5-diethylphenyl)-4,5-dihydrooxazol-2-yl)pyridine **L56** (4.8 mg, 0.01 mmol), nickel(II) acetylacetonate (2.3 mg,

0.009 mmol), cyclic sulfate (0.30 mmol) and tetrahydrofuran (0.10 mL, [substrate] = 3.0 M). The vial was sealed with a teflon septum cap, removed from dry box, placed under $N_2$ and cooled to -78 °C in dry ice/acetone bath. The Grignard reagent (1.0 M in tetrahydrofuran, 0.45 mL, 0.45 mmol) was added slowly dropwise; once addition was complete the vial was moved to a -25 °C bath and allowed to stir for 14 h.

*General cross-coupling procedure B (Dry-box free)*:

An oven dried 2-dram vial equipped with a magnetic sir bar open to air was charged successively with 2,6-bis((*R*)-4-(3,5-diethylphenyl)-4,5-dihydrooxazol-2-yl)pyridine **L56** (4.8 mg, 0.01 mmol), nickel(II) acetylacetonate (2.3 mg, 0.009 mmol), and cyclic sulfate (0.30 mmol). Reaction was sealed with a teflon septum cap and flushed with $N_2$ for 1 min before tetrahydrofuran (0.10 mL, [substrate] = 3.0 M) added. Reaction mixure was cooled to -78 °C in dry ice/acetone bath and Grignard reagent (1.0 M in tetrahydrofuran, 0.45 mL, 0.45 mmol) was added slowly dropwise; once addition was complete the vial was moved to a -25 °C bath and allowed to stir for 14 h.

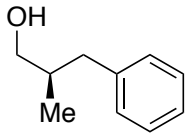
*Conversion to alcohol:*

The crude reaction mixture was transferred to a scintillation vial using diethyl ether and the solvent removed by rotary evaporation. The solid residue was then suspended in diethyl ether (6.0 mL) and aqueous sulfuric acid (20% aq, 2.0 mL) added. The mixture was allowed to vigorously stir at room temperature for 24 hours before being transfered to a seperatory funnel where it was extracted with diethyl ether (3 x 5 mL). The organic layers

were combined, dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation.

*Isolation of sulfate half-ester:*

The reaction mixture was quenched with saturated aqueous ammonium chloride (1 mL), and then extracted with ethyl acetate (5 x 5 mL). The organic layers were combined dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation.



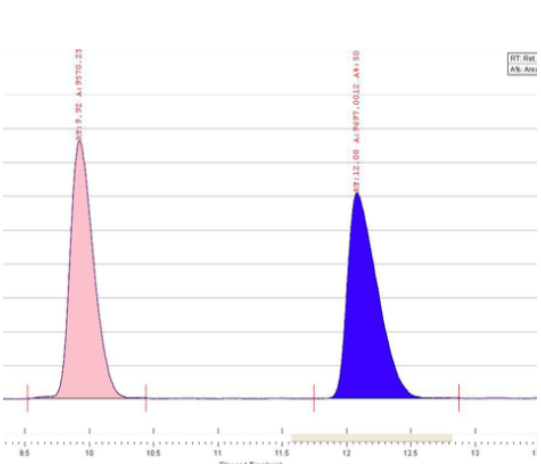

**(*R*)-2-Methyl-3-phenylpropan-1-ol.** Prepared according to the general procedure A with 5-methyl-1,3,2-dioxathiane 2,2-dioxide (**1**) and phenyl magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (4:1 pentane: diethyl ether) to afford a clear, colorless oil (36 mg, 80% yield). $R_f$ = 0.14 (3:1 pentane: diethyl ether, stain in PMA). $[\alpha]^{22}_{D}$ = 9.890 (c = 0.335, $CHCl_3$). Spectral data is in accord with the literature.[123]

***Analysis of Stereochemistry***

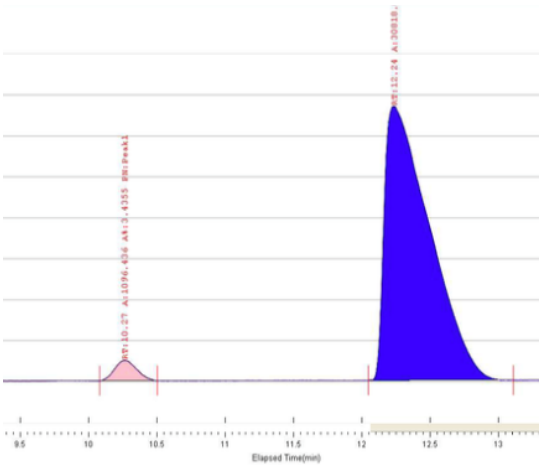
The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**.

*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 3% i-PrOH, 100 bar, 35 °C)*

[123] Szostak, M.; Spain, M.; Eberhard, A. J.; Procter, D. J. *J. Am. Chem. Soc.,* **2014**, *136*, 2268



Racemic



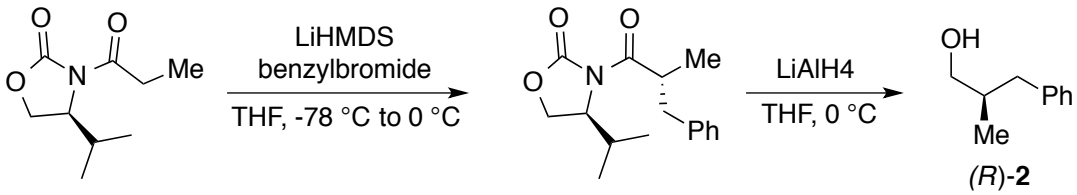
Reaction Product

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 3.4355 | 1096.436 | 10.27 | 98.5303 | 0.0096 |
| 2 | 96.5645 | 30818.0035 | 12.24 | 1338.8298 | 0.0114 |
| Total: | 100 | 31914.4395 | | | |

***Structure Proof:***

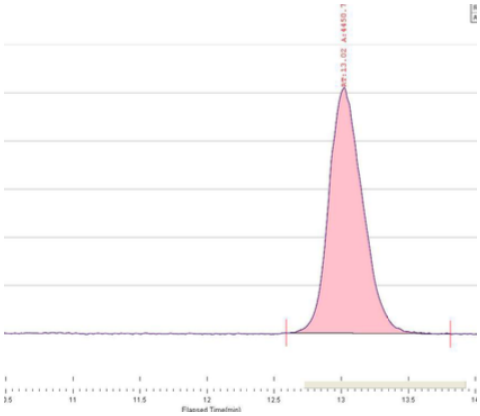
The absolute stereochemistry of **2**, was determined by comparison with the non-racemic product synthesized by asymmetric alkylation with Evans auxiliary.[124]




*(R)*-**2**

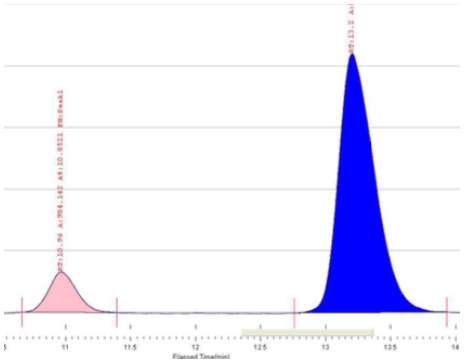
[124] Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737

*authentic product*

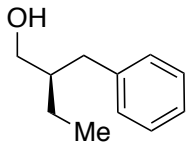


| Peak Info | | | |
|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** |
| 1 | 100 | 4450.7488 | 13.02 |
| Total: | 100 | 4450.7488 | |

*co-injection of authentic product with reaction product*



| Peak Info | | | |
|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** |
| 1 | 10.8521 | 984.142 | 10.96 |
| 2 | 89.1479 | 8084.5696 | 13.2 |
| Total: | 100 | 9068.7116 | |



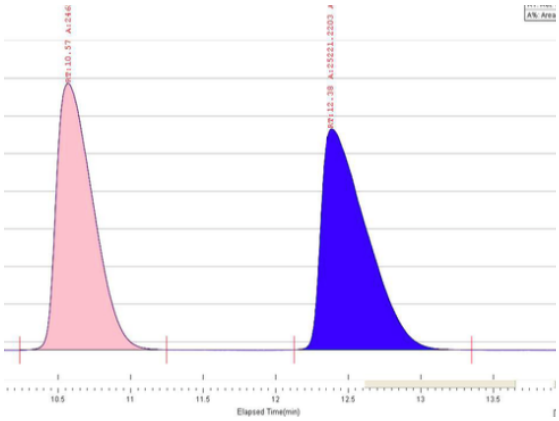

**(*R*)-2-Benzylbutan-1-ol.** Prepared according to the general procedure A with 5-ethyl-1,3,2-dioxathiane 2,2-dioxide (**SI-4**) and phenyl magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (4:1 pentane: diethyl ether) to afford a clear, colorless oil (41.8 mg, 85% yield). $R_f$ = 0.38 (3:1

pentane: diethyl ether, stain in $KMnO_4$). $[\alpha]^{22}_D$ = - 6.005 (c = 1.745, $CHCl_3$). Spectral data is in accord with the literature.[125]

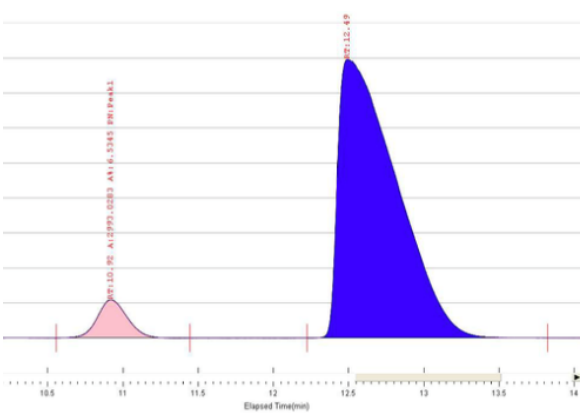
***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 3% i-PrOH, 100 bar, 35 °C)*



Racemic

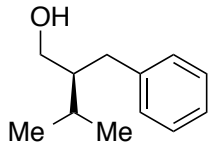


Reaction Product

[125] Cano, R.; Yus, M.; Ramon, D. J. *Chem. Comm.,* **2012**, *48*, 7628.

Peak Info

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 6.5345 | 2993.0283 | 10.92 | 218.7499 | 0.0101 |
| 2 | 93.4655 | 42810.5259 | 12.49 | 1593.6363 | 0.0115 |
| Total: | 100 | 45803.5542 | | | |



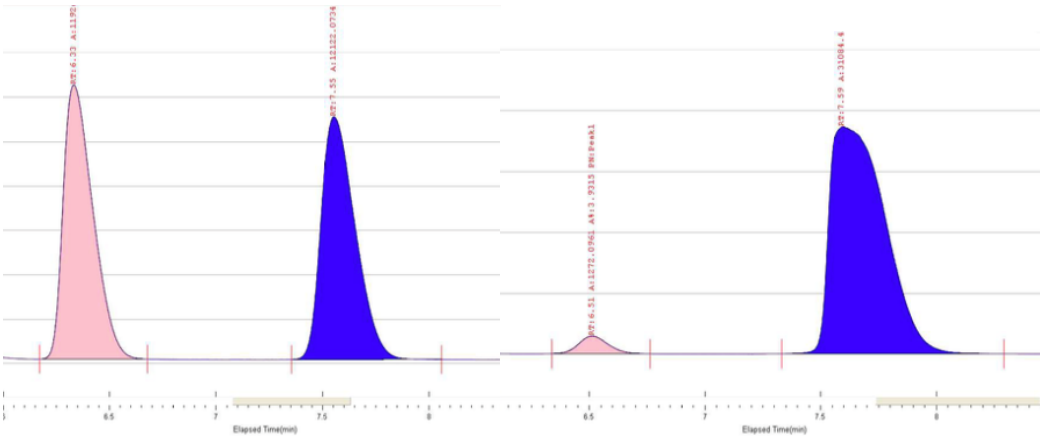

**(*S*)-2-Benzyl-3-methylbutan-1-ol.** Prepared according to the general procedure A with 5-isopropyl-1,3,2-dioxathiane 2,2-dioxide (**SI-5**) and phenyl magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (4:1 pentane: diethyl ether) to afford a clear, colorless oil (44.9 mg, 84% yield). $R_f$ = 0.23 (3:1 pentane: diethyl ether, stain in $KMnO_4$). $[\alpha]^{22}_D$ = -7.032 (c = 0.455, $CHCl_3$). Spectral data is in accord with the literature.[126]

***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

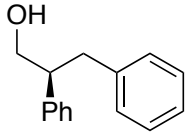
*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 5% i-PrOH, 100 bar, 35 °C)*

[126] Tietz, L. F.; Raith, C.; Brazel, C. C.; Hoelsken, S.; Magull, J. *Synthesis,* **2008**, *2*, 229.



Racemic Reaction Product

| Peak Info | | | | | |
|---|---|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** | **Height (mV)** | **K'** |
| 1 | 3.9315 | 1272.0961 | 6.51 | 145.0077 | 0.0062 |
| 2 | 96.0685 | 31084.458 | 7.59 | 1866.8998 | 0.0073 |
| Total: | 100 | 32356.5541 | | | |



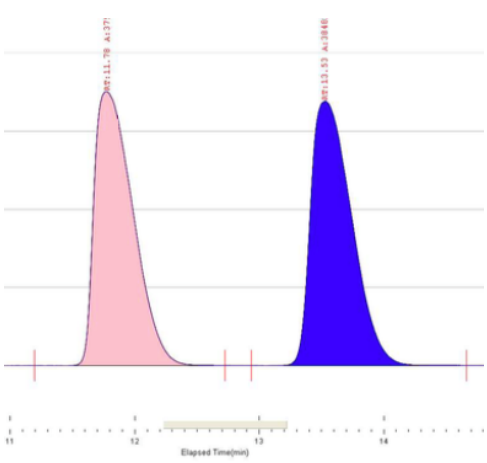

**(*S*)-2,3-Diphenylpropan-1-ol.** Prepared according to the general procedure A with 5-phenyl-1,3,2-dioxathiane 2,2-dioxide (**SI-6**) and phenyl magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (4:1 pentane: diethyl ether) to afford a clear, colorless oil (38.8 mg, 63% y). $R_f$ = 0.20 (4:1 pentane: diethyl ether, stain in PMA). $[\alpha]^{22}_D$ = 28.371 (c = 2.50, $CHCl_3$). Spectral data is in accord with the literature.[127]

[127] Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, **2011**, *133*, 4260.

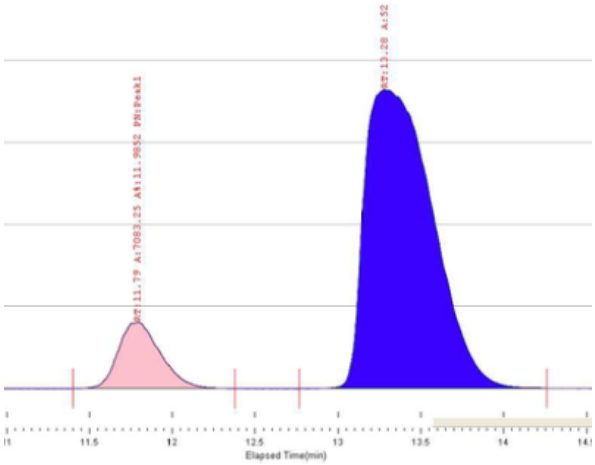
***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 7% i-PrOH, 100 bar, 35 °C)*



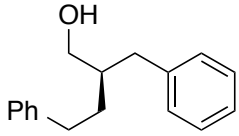
Racemic



Reaction Product

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 11.9852 | 7083.25 | 11.79 | 404.9781 | 0.0196 |
| 2 | 88.0148 | 52016.7503 | 13.28 | 1824.0935 | 0.0221 |
| Total: | 100 | 59100.0003 | | | |



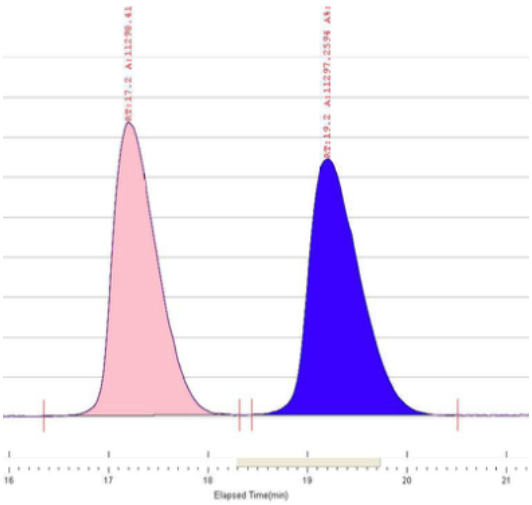

**(*R*)-2-Benzyl-4-phenylbutan-1-ol.** Prepared according to the general procedure A with 5-phenethyl-1,3,2-dioxathiane 2,2-dioxide (**SI-7**)

and phenyl magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (3:1 pentane: diethyl ether) to afford a clear, colorless oil (46.1 mg, 64% yield). $R_f$ = 0.22 (4:1 pentane: diethyl ether, stain in PMA).$^1$H NMR (600 MHz, $CDCl_3$): δ 1.65 (1H, ddt, *J* = 13.7 Hz, 9.8 Hz, 6.4 Hz), 1.74 (1H, ddt, *J* = 13.2 Hz, 9.8 Hz, 6.6 Hz), 1.86 (1H, m), 2.63- 2.71 (4H, m), 3.54- 3.60 (1H, m), 7.14- 7.20 (6H, m), 7.25- 7.29 (4H, m); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 32.5, 33.3, 37.6, 42.0, 64.7, 125.7, 125.9, 128.30, 128.32, 129.1, 140.5, 142.3; IR (neat): 3376 (br, m), 3083 (m), 3060 (m), 2923 (m), 1601 (w), 1494 (m), 1453 (m), 1029 (m), 739 (m), 698 (s) $cm^{-1}$; HRMS-(DART-TOF) for $C_7H_{19}$ [M+H-$H_2O$]: calculated: 223.14866, found: 223.14965. $[\alpha]^{22}_D$ = 14.926 (c = 1.045, $CHCl_3$).

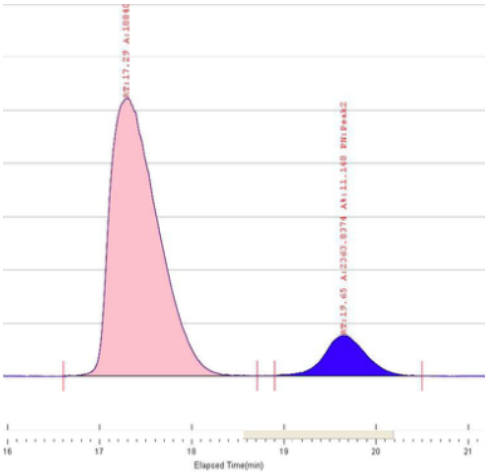
***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

*Chiral SFC (OJ-H, Chiraldex, 3 mL/ min, 6% i-PrOH, 100 bar, 35 °C)*



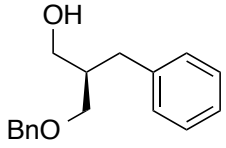
Racemic



Reaction Product

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 88.852 | 18840.3606 | 17.29 | 521.6219 | 0.0216 |
| 2 | 11.148 | 2363.8374 | 19.65 | 76.0767 | 0.0245 |
| Total: | 100 | 21204.198 | | | |



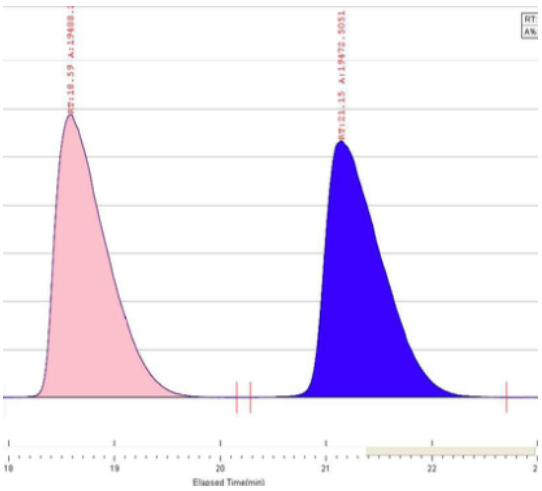

**(*R*)-2-Benzyl-3-(benzyloxy)propan-1-ol**. Prepared according to the general procedure A with 5-((benzyloxy)methyl)-1,3,2-dioxathiane 2,2-dioxide (**SI-8**) and phenyl magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (3:1 pentane: diethyl ether) to afford a clear,

colorless oil (62.2 mg, 81% yield). $R_f$ = 0.19 (3:1 pentane: diethyl ether, stain in PMA). $[\alpha]^{22}_D$ = 23.783 (c = 2.23, $CHCl_3$). Spectral data is in accord with the literature.[128]

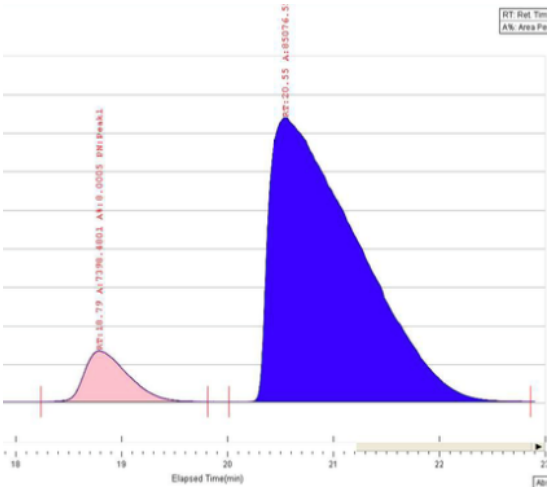
***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 6% i-PrOH, 100 bar, 35 °C)*



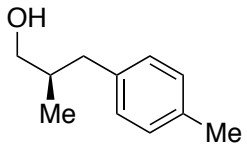
Racemic



Reaction Product

[128] Lu, D.; Sham, Y. Y.; Vince, R. *Bioorg. Med. Chem.,* **2010**, *18*, 2037.

| Peak Info | | | | | |
|---|---|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** | **Height (mV)** | **K'** |
| 1 | 8.0005 | 7398.4801 | 18.79 | 264.4453 | 0.0234 |
| 2 | 91.9995 | 85076.5525 | 20.55 | 1474.1936 | 0.0256 |
| Total: | 100 | 92475.0326 | | | |



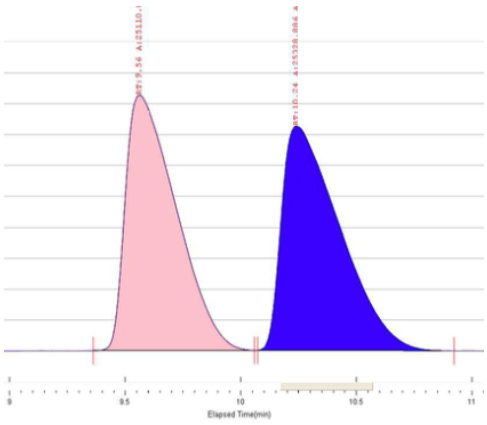

**(*R*)-2-Methyl-3-(*p*-tolyl)propan-1-ol.** Prepared according to the general procedure A with 5-methyl-1,3,2-dioxathiane 2,2-dioxide and *p*-tolylmagneisum bromide. The crude reaction mixture was purified by silica gel chromatography (4:1 pentane: diethyl ether) to afford a clear, colorless oil (48.2 mg, 98% yield). $R_f$ = 0.21 (4:1 pentane: diethyl ether, stain in $KMnO_4$). $[\alpha]^{22}_D$ = 11.633 (c = 1.860, $CHCl_3$). Spectral data is in accord with the literature.[129]

***Analysis of Stereochemistry:***

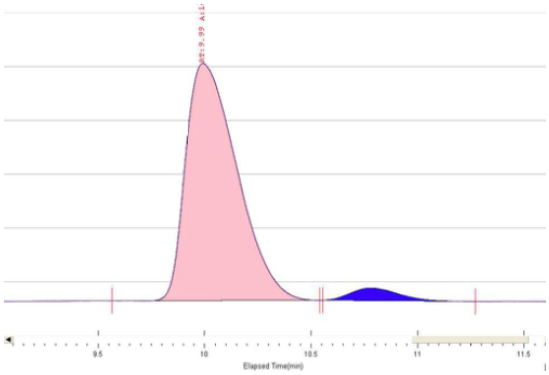
The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

[129] Dikusar, P.; Zhukovskaya, M.; Petkcevich, K.; Zolotar, C. *Russ. J. Gen. Chem.,* **2014**, *84,* 1179.

*Chiral SFC (AD-H, Chiraldex, 3 mL/ min, 3% i-PrOH, 100 bar, 35 °C)*



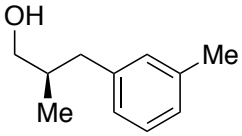
Racemic



Reaction Product

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 95.2979 | 14741.7921 | 9.99 | 883.5606 | 0.0115 |
| 2 | 4.7021 | 727.3792 | 0 | 59.0586 | 0 |
| Total: | 100 | 15469.1713 | | | |



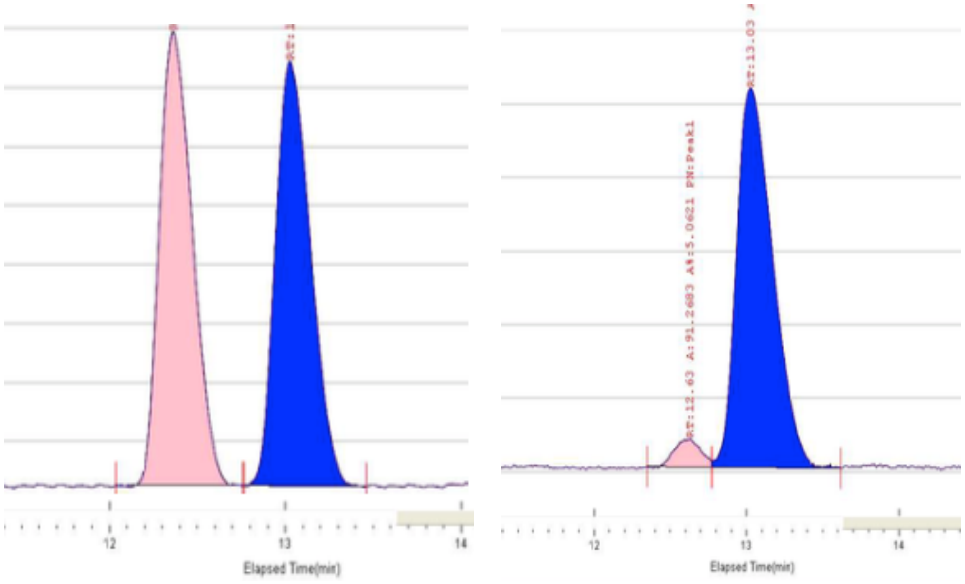

**(*R*)-2-Methyl-3-(*m*-tolyl)propan-1-ol.** Prepared according to the general procedure A with 5-phenethyl-1,3,2-dioxathiane 2,2-dioxide and *m*-tolylmagnesium bromide. The crude reaction mixture was purified by silica gel chromatography (4:1 pentane: diethyl ether) to afford a clear, colorless oil (40.9 mg, 83% yield). $R_f$ = 0.20 (4:1 pentane: diethyl ether, stain in PMA).$^1$H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, d, *J* = 6.8 Hz), 1.91- 1.99 (1H, m), 2.33 (3H, s), 2.39 (1H, dd, *J* = 13.6 Hz, 8.0 Hz), 2.71 (1H, dd, *J* = 13.2 Hz, 6.4 Hz), 3.47 (1H, dd, *J* = 10.8 Hz, 4.8 Hz), 6.96- 7.02 (2H, m), 7.17 (1H, t, *J* = 7.2 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 16.5, 21.4, 37.8, 39.7, 67.7, 126.1, 126.6,

128.1, 129.9, 137.8, 140.6; IR (neat): 3333 (br), 3018 (w), 2954 (m), 2920 (m), 2870 (m), 1608 (w), 1457 (m), 1033 (s), 740 (m), 699 (m) $cm^{-1}$; HRMS-(DART-TOF) for $C_{11}H_{15}$ [M+H-$H_2O$]: calculated: 147.11738, found: 147.11713. $[\alpha]^{22}_D$ = 11.490 (c = 0.905, $CHCl_3$).

***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

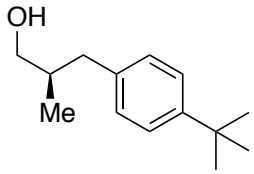
*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 3% i-PrOH, 100 bar, 35 °C)*




Racemic

Reaction Product

| Peak Info | | | | | |
|---|---|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** | **Height (mV)** | **K'** |
| 1 | 5.0621 | 91.2683 | 12.63 | 7.7537 | 0.0144 |
| 2 | 94.9379 | 1711.7186 | 13.03 | 103.2822 | 0.0149 |
| Total: | 100 | 1802.9869 | | | |



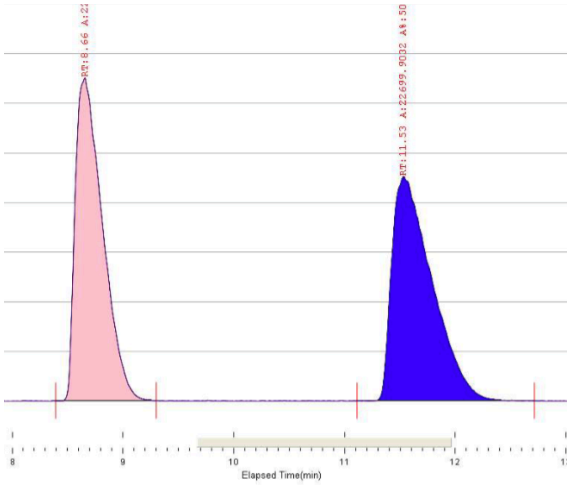

**(*R*)-3-(4-(*tert*-butyl)phenyl)-2-methylpropan-1-ol.** Prepared according to the general procedure A with 5-methyl-1,3,2-dioxathiane 2,2-dioxide and (4-(*tert*-butyl)phenyl)magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (4:1 pentane: diethyl ether) to afford a light yellow oil (55.7 mg, 90% yield). $R_f$ = 0.20 (4:1 pentane: diethyl ether, stain in PMA). $[\alpha]^{22}_D$ = 8.819 (c = 2.680, $CHCl_3$). Spectral data is in accord with the literature.[130]

***Analysis of Stereochemistry:***

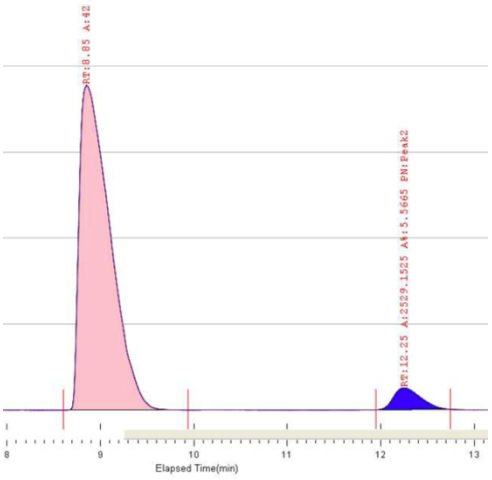
The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

[130] Noonan, G. M.; Fuentes, J. A.; Cobley, C. J.; Clarke, M. L. *Angew. Chem. Int. Ed.,* **2012**, *51*, 2477.

*Chiral SFC (AD-H, Chiraldex, 3 mL/ min, 3% i-PrOH, 100 bar, 35 °C)*



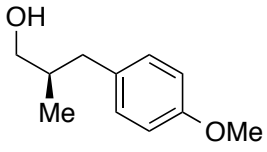

Racemic




Reaction Product

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 94.4335 | 42906.1081 | 8.85 | 1890.3124 | 0.0098 |
| 2 | 5.5665 | 2529.1525 | 12.25 | 127.1905 | 0.0136 |
| Total: | 100 | 45435.2606 | | | |



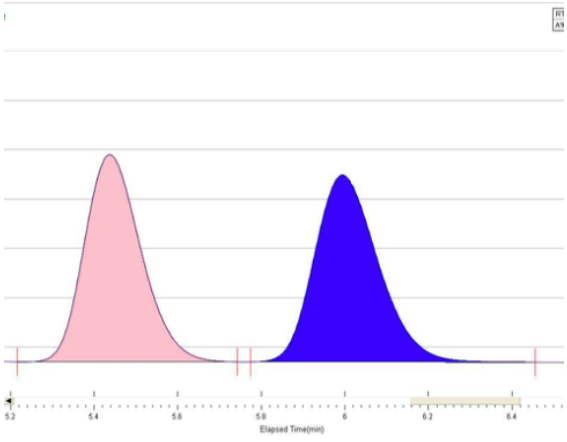

**(*R*)-3-(4-Methoxyphenyl)-2-methylpropan-1-ol.** Prepared according to the general procedure A with 5-methyl-1,3,2-dioxathiane 2,2-dioxide and (4-methoxyphenyl)magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (4:1 pentane: diethyl ether) to afford a

light yellow oil (43.2 mg, 80% yield). $R_f$ = 0.19 (3:1 pentane: diethyl ether, stain in PMA). $[\alpha]^{22}_D$ = 9.412 (c = 0.425, $CHCl_3$). Spectral data is in accord with the literature.[131]

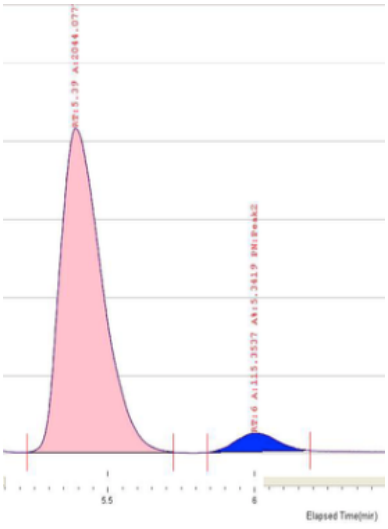
***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 8% i-PrOH, 100 bar, 35 °C)*



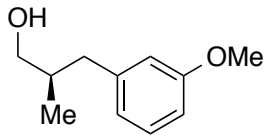
Racemic



Reaction Product

[131] Beghetto, V.; Scrivanti, A.; Bertoldini, M.; Aversa, M.; Zancanaro, A.; Matteoli, U. *Synthesis.* **2015**, *47*, 272.

| Peak Info | | | | | |
|---|---|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** | **Height (mV)** | **K'** |
| 1 | 94.6581 | 2044.0777 | 5.39 | 208.0036 | 0.0068 |
| 2 | 5.3419 | 115.3537 | 6 | 11.8315 | 0.0076 |
| Total: | 100 | 2159.4314 | | | |



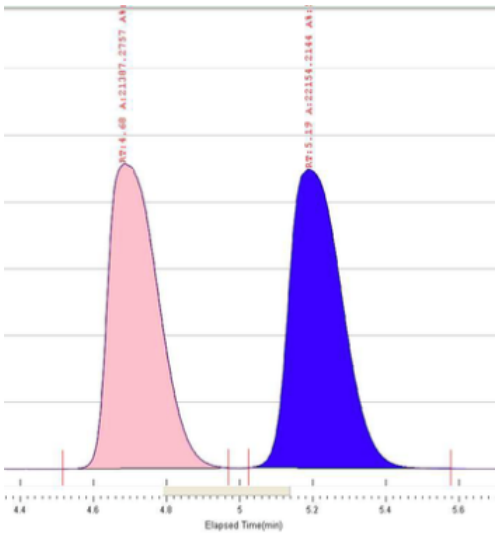

**(*R*)-3-(3-Methoxyphenyl)-2-methylpropan-1-ol.** Prepared according to the general procedure A with 5-methyl-1,3,2-dioxathiane 2,2-dioxide and (3-methoxyphenyl)magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (3:1 pentane: diethyl ether) to afford a light yellow oil (46.5 mg, 86% yield). $R_f$ = 0.15 (3:1 pentane: diethyl ether, stain in PMA). $[\alpha]^{22}_D$ = 10.520 (c = 0.765, $CHCl_3$). Spectral data is in accord with the literature.[132]

***Analysis of Stereochemistry:***

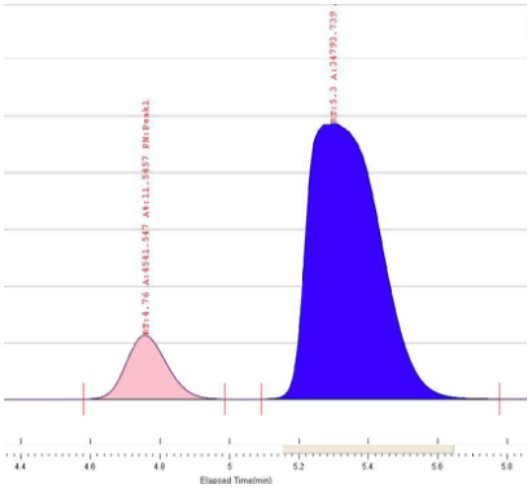
The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 12% i-PrOH, 100 bar, 35 °C)*

[132] Brenna, E.; Fronza, G.; Fuganti, C.; Gatti, F. G.; Manfredi, A.; Parmeggiani, F.; Ronchi, P. *J. Mol. Cat. B: Enzym.,* **2012**, *84*, 94.



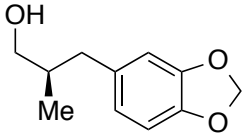
Racemic



Reaction Product

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 11.5457 | 4541.547 | 4.76 | 562.3258 | 0.0059 |
| 2 | 88.4543 | 34793.739 | 5.3 | 2427.3042 | 0.0066 |
| Total: | 100 | 39335.286 | | | |



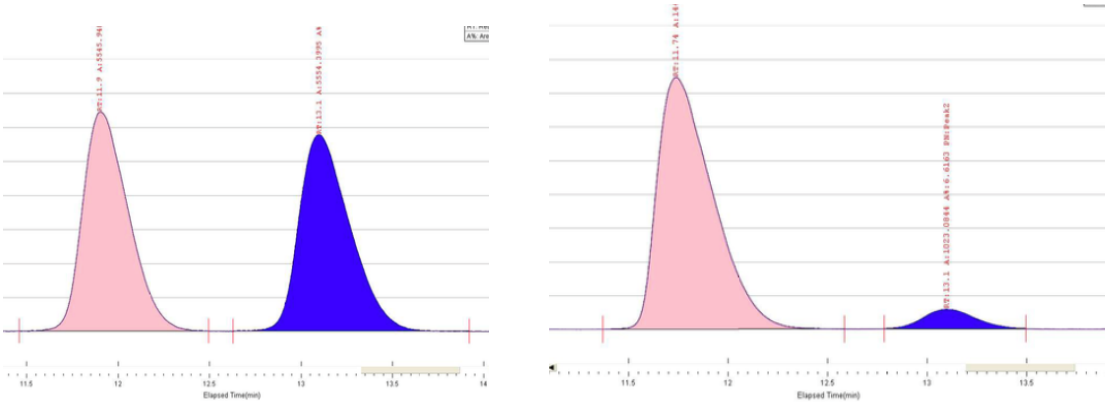

**(*R*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-2-methylpropan-1-ol.** Prepared according to the general procedure A with 5-methyl-1,3,2-dioxathiane 2,2-dioxide and benzo[*d*][1,3]dioxol-5-ylmagnesium bromide. The crude reaction mixture was purified by silica gel chromatography (3:1 pentane: diethyl ether) to afford a light yellow oil (47.2 mg, 81% yield). $R_f$ = 0.10 (3:1 pentane: diethyl ether, stain in $KMnO_4$). $[\alpha]^{22}_D$ = 12.131 (c = 1.940, $CHCl_3$). Spectral data is in accord with the literature.[133]

[133] Enders, D.; Backes, M. *Tetrahedron: Asymmetry*, **2004**, *15*, 1813.

***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

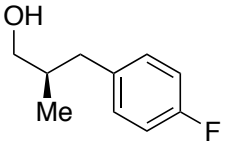
*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 4% i-PrOH, 100 bar, 35 °C)*



Racemic

Reaction Product

| Peak Info | | | | | |
|---|---|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** | **Height (mV)** | **K'** |
| 1 | 93.3837 | 14439.946 | 11.74 | 746.7883 | 0.013 |
| 2 | 6.6163 | 1023.0844 | 13.1 | 57.204 | 0.0145 |
| Total: | 100 | 15463.0304 | | | |



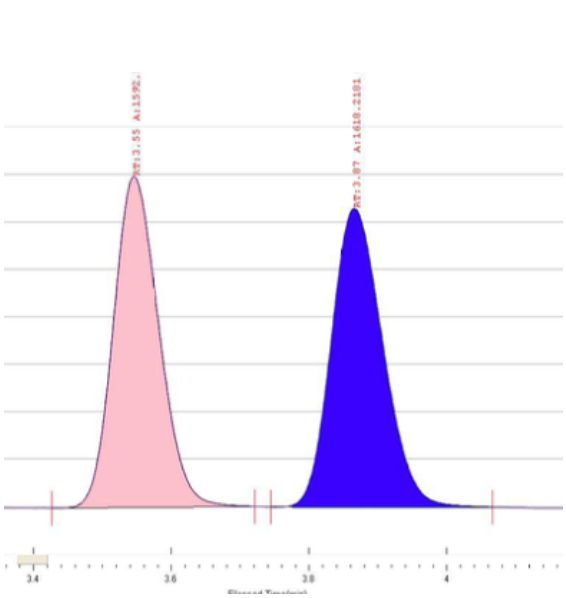

**(*R*)-3-(4-Fluorophenyl)-2-methylpropan-1-ol.** Prepared according to the general procedure A with 5-methyl-1,3,2-dioxathiane 2,2-dioxide and (4-fluorophenyl)magnesium bromide, with increased catalyst loading $Ni(acac)_2$ (6 mol%), **L56** (6.6 mol%). The crude reaction mixture was purified by silica gel

chromatography (3:1 pentane: diethyl ether) to afford a clear, colorless oil (45.9 mg, 91% yield). $R_f$ = 0.08 (4:1 pentane: diethyl ether, stain in PMA). $[\alpha]^{22}_D$ = 12.479 (c = 0.910, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): δ 0.90 (3H, d, *J* = 6.5 Hz), 1.30 (1H, bs), 2.40 (1H, dd, *J* = 13.5 Hz, 8.0 Hz), 2.74 (1H, dd, *J* = 14.0 Hz, 6.5 Hz), 3.47- 3.51 (2H, m), 6.92- 7.01 (2H, m), 7.12 (2H, ddd, J = 8.4 Hz, 5.2 Hz, 2.4 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 16.3, 37.7, 38.7, 67.4, 114.9 (d, $J_{CF}$= 21.0 Hz), 130.4 (d, $J_{CF}$= 7.5 Hz), 136.1 (d, $J_{CF}$= 4.0 Hz), 161.3 (d, $J_{CF}$= 242 Hz); IR (neat): 3342 (br), 2965 (m), 2920 (m), 2873 (m), 1509 (s), 1157 (s), 985 (m), 834 (m) $cm^{-1}$; HRMS-(DART-TOF) for $C_{10}H_{14}F_1O_5$[M+H]: calculated: 169.10287, found: 169.10287.

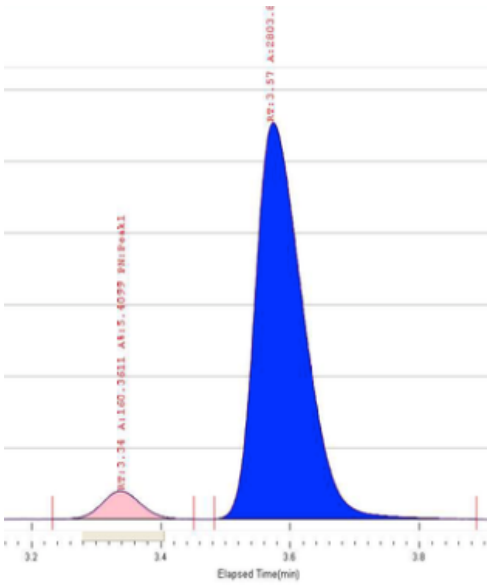
***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

*Chiral SFC (AS-H, Chiraldex, 3 mL/ min, 3% i-PrOH, 100 bar, 35 °C)*



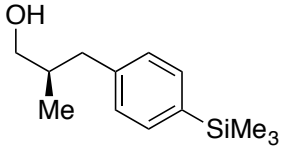
Racemic




Reaction Product

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 5.4099 | 160.3611 | 3.34 | 39.0406 | 0.0043 |
| 2 | 94.5901 | 2803.8527 | 3.57 | 553.5303 | 0.0046 |
| Total: | 100 | 2964.2138 | | | |



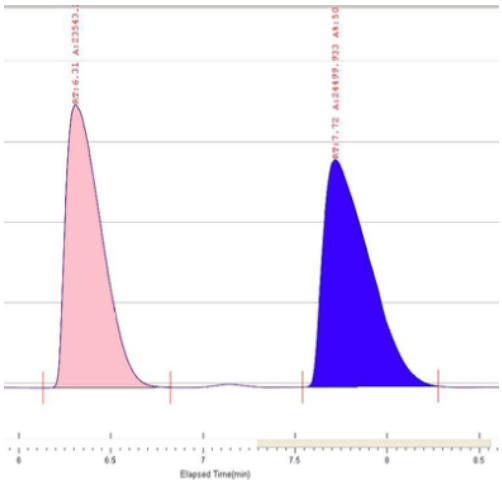

**(*R*)-2-Methyl-3-(4-(trimethylsilyl)phenyl)propan-1-ol.** Prepared according to the general procedure A with 5-methyl-1,3,2-dioxathiane 2,2-dioxide and (4-(trimethylsilyl)phenyl)magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (5:1 pentane: diethyl ether) to afford a clear, colorless oil (61.9 mg, 93% yield). $R_f$ = 0.38 (5:1 pentane: diethyl ether, stain

in $KMnO_4$). $[\alpha]^{22}_D$ = 6.114 (c = 2.525, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$): δ 0.26 (9H, s), 0.93 (3H, d, *J* = 6.6 Hz), 1.96 (1H, dq, *J* = 12.6 Hz, 6.6 Hz), 2.42 (1H, dd, *J* = 13.2 Hz, 8.4 Hz), 2.75 (1H, dd, *J* = 13.2 Hz, 6.6 Hz), 3.47- 3.50 (1H, m), 3.52- 3.56 (1H, m), 7.17 (d, *J* = 8.4 Hz), 7.44 (2H, d, *J* = 8.4 Hz); $^{13}$C NMR (151 MHz, $CDCl_3$): δ 1.1, 16.5, 39.7, 67.6, 128.6, 133.3, 137.5, 141.2; IR (neat): 3341 (br), 2954 (m), 2920 (m), 1458 (m), 1034 (m), 852 (s), 836 (s) $cm^{-1}$; HRMS-(DART-TOF) for $C_{13}H_{21}Si_1$[M+H-$H_2O$]: calculated: 205.14125, found: 205.14023.

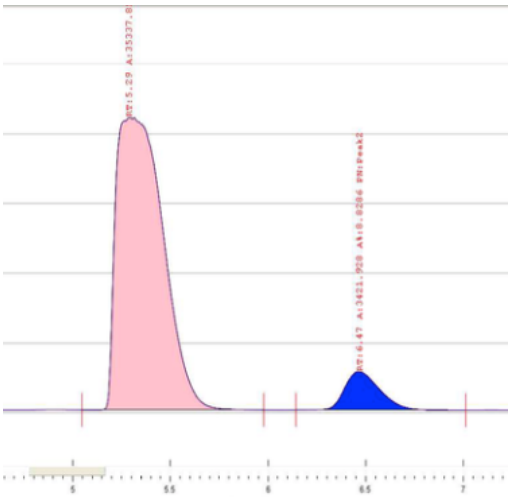
***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

*Chiral SFC (AD-H, Chiraldex, 3 mL/ min, 3% i-PrOH, 100 bar, 35 °C)*

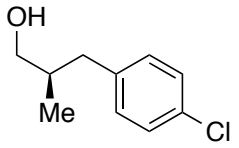


Racemic



Reaction Product

| Peak Info | | | | | |
|---|---|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** | **Height (mV)** | **K'** |
| 1 | 91.1714 | 35337.8521 | 5.29 | 2099.4284 | 0.008 |
| 2 | 8.8286 | 3421.928 | 6.47 | 276.6675 | 0.0098 |
| Total: | 100 | 38759.7801 | | | |



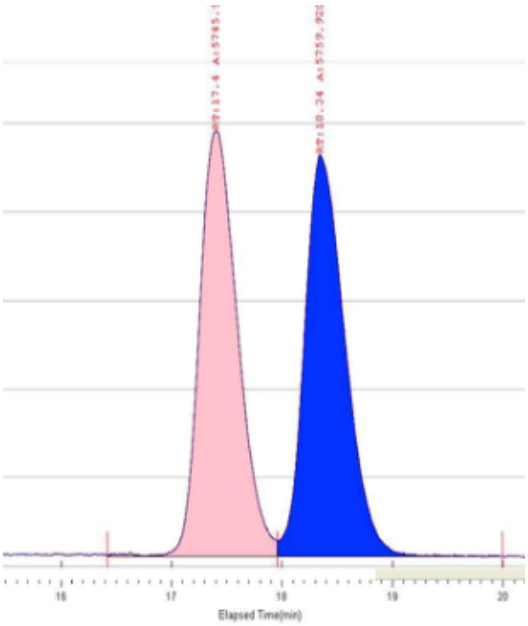

**(*R*)-3-(4-chlorophenyl)-2-methylpropan-1-ol**. Prepared according to the general procedure A with 5-methyl-1,3,2-dioxathiane 2,2-dioxide and *p*-chloromagneisum bromide. The crude reaction mixture was purified by silica gel chromatography (3:1 pentane: diethyl ether) to afford a clear, colorless oil (32.4 mg, 59% yield). $R_f$ = 0.14 (3:1 pentane: diethyl ether, stain in $KMnO_4$). $[\alpha]^{22}_D$ = 8.032 (c = 1.620, $CHCl_3$). Spectral data is in accord with the literature.[134]

***Analysis of Stereochemistry:***

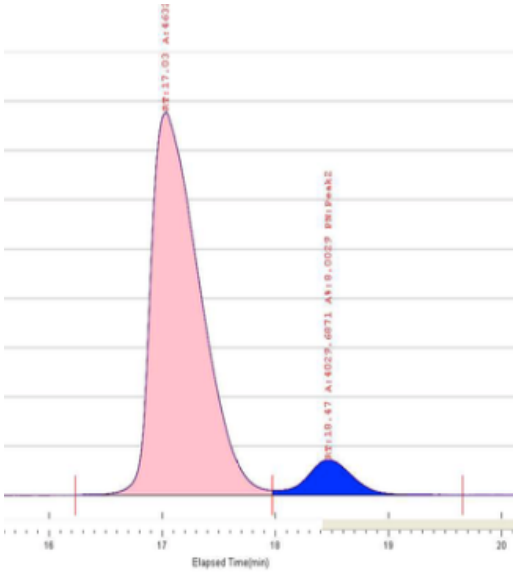
The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

[134] Brenna, E.; Fronza, G.; Fuganti, C.; Gatti, F. G.; Manfredi, A.; Parameggiani, F.; Ronchi, P. *J. Mol. Catal. B: Enzym*. **2012**, *84*, 94.

*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 2% i-PrOH, 100 bar, 35 °C)*



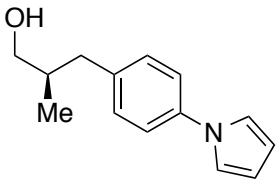
Racemic



Reaction Product

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 91.9971 | 46322.9177 | 17.03 | 1554.4752 | 0.0179 |
| 2 | 8.0029 | 4029.6871 | 18.47 | 142.4697 | 0.0194 |
| Total: | 100 | 50352.6048 | | | |



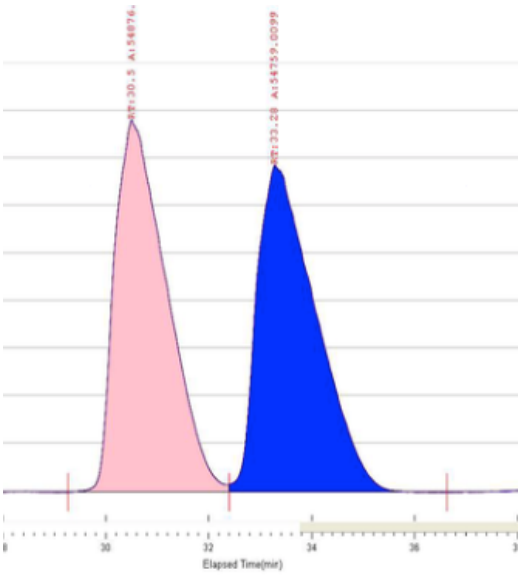

**(*R*)-3-(4-(1*H*-pyrrol-1-yl)phenyl)-2-methylpropan-1-ol.** Prepared according to the general procedure A with 5-phenethyl-1,3,2-dioxathiane 2,2-dioxide and (4-(1*H*-pyrrol-1-yl)phenyl)magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (2:1 pentane: diethyl ether) to afford a clear, beige solid (45.2 mg, 68% yield). $R_f$ = 0.14 (2:1 pentane: diethyl ether, stain in $KMnO_4$). $^1$H NMR (500 MHz, $CDCl_3$): δ

0.94 (3H, d, J = 6.5 Hz), 1.40 (1H, s), 1.93-1.99 (m), 2.45 (1H, dd, J = 8.0 Hz, 13.5 Hz), 2.80 (1H, dd, J = 6.5 Hz, 13.5 Hz), 3.53 (1H, qd, J = 6.0 Hz, 10.5 Hz), 6.34 (2H, s), 7.07 (2H, s), 7.22 (2H, d, J = 8.0 Hz), 7.32 (2H, d, J = 8.0 Hz); $^{13}$C NMR (151 MHz, $CDCl_3$): δ 16.5, 37.9, 39.1, 67.6, 110.3, 119.5, 120.6, 130.3, 138.2, 139.0; IR (neat): 3362 (br), 2954 (w), 2920 (w), 1520 (s), 1480 (w), 1326 (m), 1020 (m), 722 (s) $cm^{-1}$; HRMS-(DART-TOF) for $C_{14}H_{18}NO$ [M+H]: calculated: 216.13884, found: 216.13938. $[\alpha]^{22}_D$ = 8.251 (c = 1.46, $CHCl_3$).

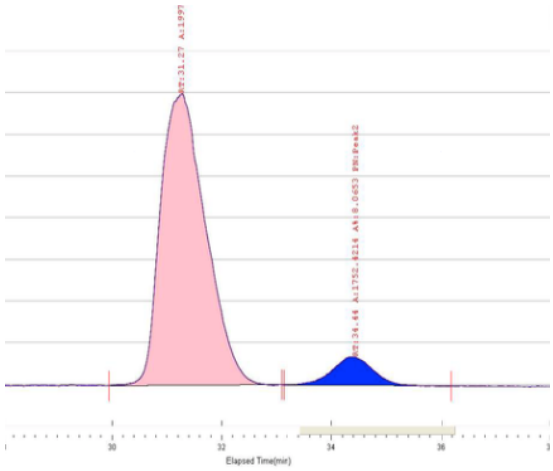
***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

*Chiral SFC (OJ-H, Chiraldex, 3 mL/ min, 2% i-PrOH, 100 bar, 35 °C)*



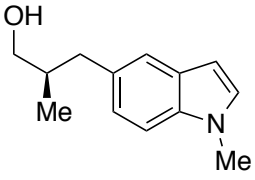
Racemic



Reaction Product

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 91.9347 | 19975.4166 | 31.27 | 349.5842 | 0.0415 |
| 2 | 8.0653 | 1752.4214 | 34.44 | 34.3977 | 0.0457 |
| Total: | 100 | 21727.838 | | | |



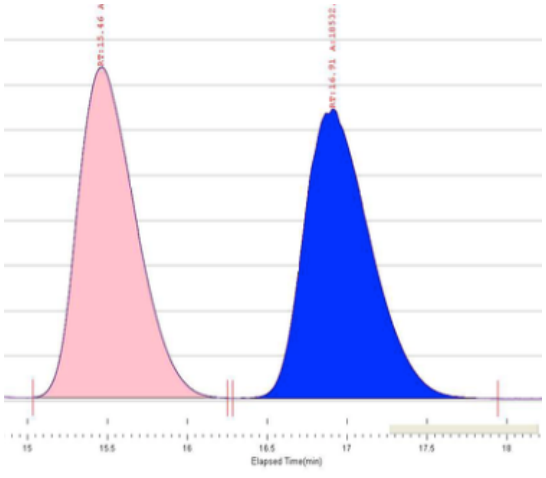

**(*R*)-2-methyl-3-(1-methyl-1*H*-indol-5-yl)propan-1-ol.** Prepared according to the general procedure A with 5-phenethyl-1,3,2-dioxathiane 2,2-dioxide and (1-methyl-1*H*-indol-5-yl)magnesium bromide. The crude reaction mixture was purified by silica gel chromatography (5:1 pentane: diethyl ether) to afford a light yellow oil (36 mg, 60% yield). $R_f$ = 0.12 (2:1 pentane: diethyl ether, stain in $KMnO_4$). $^1$H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, d, *J* = 6.7 Hz), 2.00 (1H, dq, *J* = 6.4 Hz, 13.2 Hz), 2.56 (1H, dd, *J* = 7.7 Hz, 13.5 Hz), 2.82 (1H, dd, *J* = 6.6 Hz, 13.5 Hz), 3.30 – 3.63 (2H, m), 6.42 (1H, d, *J* = 2.9 Hz), 7.02 (1H, d, *J* = 2.9 Hz), 7.05 (1H, d, *J* = 8.2 Hz), 7.25 (1H, m), 7.41 (1H, s); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 16.7, 32.8, 38.3,

39.9, 67.9, 100.4, 108.9, 120.8, 123.0, 128.6, 128.9, 131.2, 135.4; IR (neat): 3394 (br), 3024 (m), 2955 (m), 2873 (m), 1706 (w), 1454 (w), 1388 (s), 915 (w), 877 (m) $cm^{-1}$; HRMS-(DART-TOF) for $C_{13}H_{18}NO$ [M+H]: calculated: 204.13884, found: 204.13864. $[\alpha]^{22}_{D}$ = 8.971 (c = 2.05, $CHCl_3$).

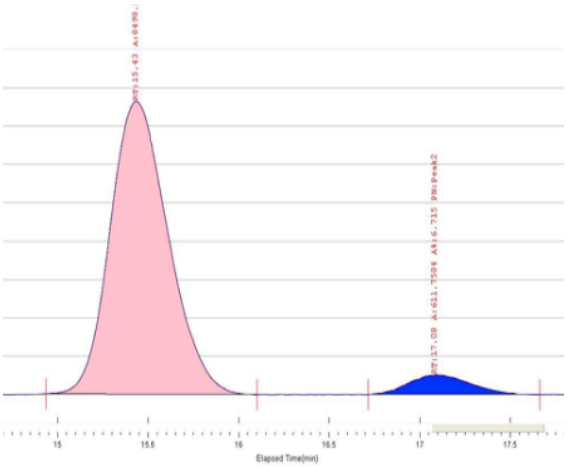
***Analysis of Stereochemistry:***

The enantioselectivity was determined by SFC analysis of the title compound in comparison to racemic material. Racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R,R)*-**L56**. Absolute stereochemistry assigned by analogy.

*Chiral SFC (AD-H, Chiraldex, 3 mL/ min, 8% i-PrOH, 100 bar, 35 °C)*

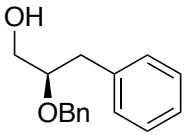


Racemic



Reaction Product

| Peak Info | | | | | |
|---|---|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** | **Height (mV)** | **K'** |
| 1 | 93.285 | 8498.5788 | 15.43 | 381.6864 | 0.0186 |
| 2 | 6.715 | 611.7584 | 17.08 | 25.6479 | 0.0206 |
| Total: | 100 | 9110.3372 | | | |



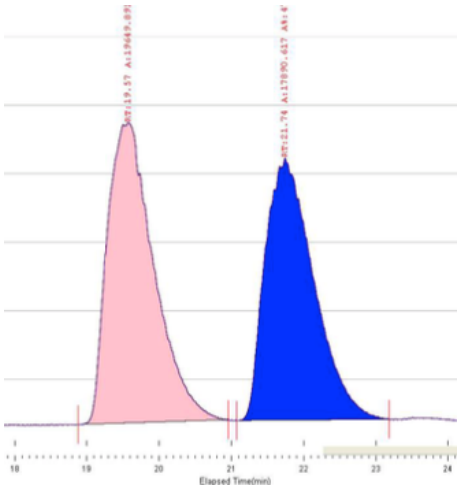

**(*R*)-2-(Benzyloxy)-3-phenylpropan-1-ol.** Prepared according to the general procedure A with 5-(benzyloxy)-1,3,2-dioxathiane 2,2-dioxide and phneylmagnesium bromide, with increased catalyst loading ($Ni(acac)_2$ (6 mol %), **L56** (6.6 mol %)). The crude reaction mixture was purified by silica gel chromatography (3:1 hexane: ethyl acetate) to afford a clear, colorless oil (48.4 mg, 68% yield). $R_f$ = 0.33 (3:1 hexane: ethyl acetate, stain in $KMnO_4$). $[\alpha]^{22}_D$ = 5.593 (c = 1.430, $CHCl_3$). Spectral data is in accord with the literature.[135]

***Analysis of Stereochemistry:***

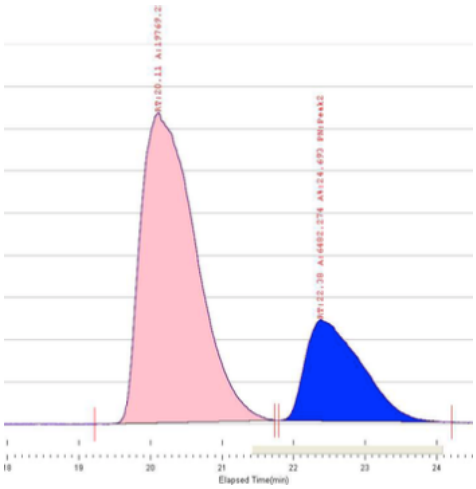
The enantioselectivity was determined by SFC analysis of the title compound compared to racemic material. Analogous racemic material was prepared using CuCl (3 mol %) in the cross coupling reaction, instead of $Ni(acac)_2$ and *(R)*-**L5**. Absolute stereochemistry was assigned by comparing optical rotation to literature, $[\alpha]^{22}_D$ = 13.50 (c = 0.65, $CHCl_3$).[136]

*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 4% i-PrOH, 100 bar, 35 °C)*

[135] Lubin, H.; Tessier, A.; Chaume, G.; Pytkowicz, J.; Brigaud, T. B. *Org. Lett.,* **2010**, *12*, 1496
[136] Sone, H.; Shibata, T.; Fujita, T.; Ojika, M.; Yamada, K. *J. Am. Chem. Soc.,* **1996**, *118*, 1874



Racemic

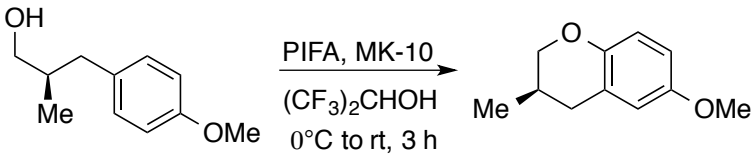


Reaction Product

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 75.307 | 19769.2357 | 20.11 | 367.8295 | 0.0208 |
| 2 | 24.693 | 6482.274 | 22.38 | 120.4728 | 0.0231 |
| Total: | 100 | 26251.5097 | | | |

### *3.7.2.5 Synthesis of (R)-6-Methoxy-3-Methylchromane*




**(*R*)-6-Methoxy-3-methylchromane.** Prepared according to the literature procedure with slight modification.[137] To a stirred solution of the alcohol (**11**, 30.0 mg, 0.16 mmol) at 0

[137] Hata, K.; Hamamoto, H.; Shiozaki, Y.; Cammerer, S. B.; Kita, Y. *Tetrahedron.* **2007**, *63,* 4052.

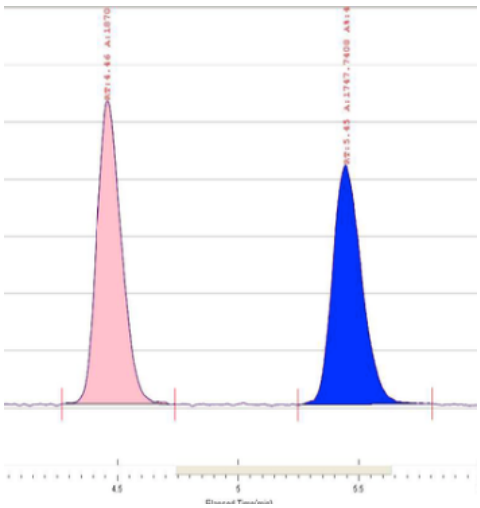
°C in $(CF_3)_2CHOH$ (1.0 mL) was added Montmorillonite K10 (80 mg) and [bis(trifluoroacetoxy)iodo]benzene (72.2 mg, 0.17 mmol). Stirring was continued for 2 h at rt. The solution was then filtered and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel chromatography (pentane to 30:1 pentane: diethyl ether) to afford a white solid (14.9 mg, 53 %). $R_f$ = 0.80 (3:1 pentane: diethyl ether, stain in PMA). $[\alpha]^{22}_D$ = - 15.185 (c = 0.59, $CDCl_3$). Spectral data is in accord with the literature.[138]

*Analysis of Stereochemistry:*

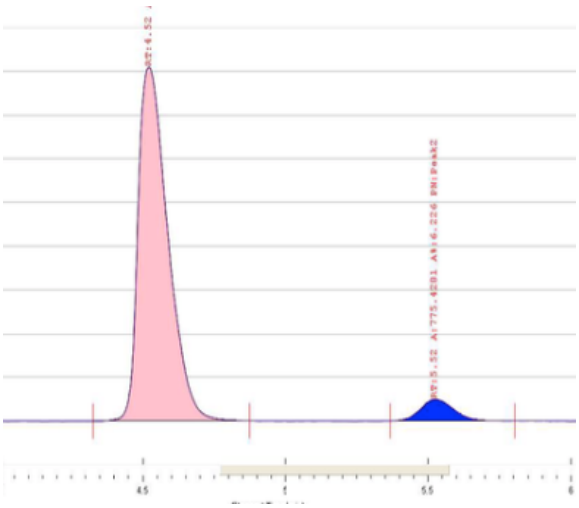
The enantioselectivity was determined by SFC analysis of the title compound compared to racemic material. Analogous racemic material was prepared using *rac*-**11** which was prepared *via* the general cross coupling procedure with CuCl (3 mol %), instead of $Ni(acac)_2$ and *(R)*-**L5**.

[138] Rajesh, T.; Das, S. *Tetrahedron*. **1997**, *53*, 16817

*Chiral SFC (OD-H, Chiraldex, 3 mL/ min, 3% i-PrOH, 100 bar, 35 °C)*



Racemic

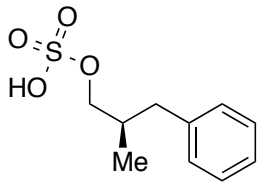


Reaction Product

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 93.774 | 11679.3104 | 4.52 | 1620.8717 | 0.0069 |
| 2 | 6.226 | 775.4281 | 5.52 | 98.2879 | 0.0084 |
| Total: | 100 | 12454.7385 | | | |

### *3.7.2.6 Gram-Scale Cross-Coupling*

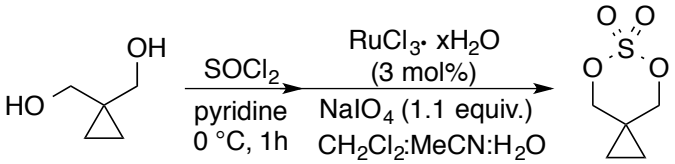



**(*R*)-2-Methyl-3-phenylpropyl hydrogen sulfate.** Prepared according to the general cross-coupling procedure with isolation of the sulfate half ester with the following changes. Reaction was conducted in an oven dried 50 mL round bottom flask with 5-methyl-1,3,2-dioxathiane 2,2-dioxide (**1**) (1.00 g, 6.60 mmol). Phenyl magnesium bromide (9.90 mL, 9.90 mmol) was added dropwise at -78 °C over 1 h before being warmed to –25 °C and allowed to stir for

15 h. The crude reaction mixture was purified by silica gel chromatography (ethyl acetate to 10% MeOH in ethyl acetate) to afford a light yellow solid (1.43 g, 92 %). $R_f$ = 0.08 (20% MeOH in EtOAc, stain in $KMnO_4$). $^1H$ NMR (500 MHz, $CD_3OD$): δ 0.92 (3H, d, *J* = 7.0 Hz), 2.06– 2.13 (1H, m), 2.43 (1H, dd, *J* = 13.5 Hz, 8.5 Hz), 2.81 (1H, dd, *J* = 13.5 Hz, 6.0 Hz), 3.82– 3.90 (1H, m), 7.14- 7.19 (3H, m), 7.28 (2H, t, J= 7.0 Hz); $^{13}C$ NMR (151 MHz, $CD_3OD$): 16.9, 36.7, 40.6, 73.5, 127.1, 129.4, 130.4, 141.7; IR (neat): 3434 (br), 3063 (m), 1241 (m), 1214 (m), 942 $cm^{-1}$; HRMS-(DART-TOF) for $C_{10}H_{18}NO_4S$ $[M+NH_4]$: calculated: 248.09565, found: 248.09624. $[\alpha]^{22}_D$ = - 4.440 (c = 1.45, $CH_3OH$).

### *3.7.2.7 Mechanistic Experiments*

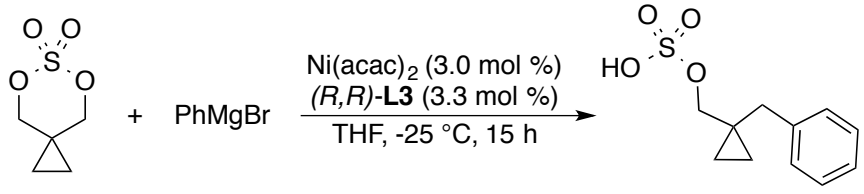
*Radical Probe:*




**5,7-Dioxa-6-thiaspiro[2.5]octane 6,6-dioxide**. Prepared according to the literature procedure with slight modification.[139] To an oven dried 25 mL round bottom flask with stir bar containing a solution of diol (0.95 mL, 10.0 mmol) in dry pyridine (10.0 mL) under $N_2$ at 0 °C was added thionyl chloride (1.45 mL, 20.0 mmol) dropwise. The reaction was then allowed to stir at 0 °C for 1 h before diethyl ether was added, the pyridine HCl salt

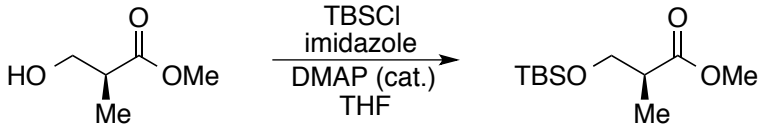
[139] Itoh, O.; Kohmura, Y.; Ichikawa, Y.; Umezu, M.; Okita, T.; Ichikawa, K. *Bull. Chem. Soc. Jpn.*, **1980**, *53*, 146.

was then removed by filtration. The filtrate was then concentrated by rotary evaporation to yield a crude solid, which was suspended in diethyl ether and washed with the following: 6M HCl (10 mL), saturated sodium bicarbonate (10 mL), and water (10 mL). The organic layer was then dried over sodium sulfate and the solvent removed by rotary evaporation. The crude product was then dissolved in $CH_2Cl_2$, MeCN, and water (1:1:2) and cooled to 0 °C. To this solution was added ruthenium chloride hydrate (3 mol%) and sodium periodate (1.1 equiv.) in portions. The solution was then allowed to warm to room temperature and stir for 30 min. The reaction was then diluted with diethyl ether and the organic layer was subsequently washed with the following: water (2 x 5 mL), saturated sodium bicarbonate (5 mL), and saturated sodium chloride solution (5 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation. The crude reaction product was purified by silica gel chromatography in 2:1 hexane: ethyl acetate to afford the desired product as a white solid (1.28 g, 78% yield). $R_f$ = 0.27 (2:1 hexane: ethyl acetate, stain in $KMnO_4$). $^1$H NMR (500 MHz, $CDCl_3$): δ 0.87 (4H, m), 4.43 (4H, m); $^{13}$C NMR (151 MHz, $CDCl_3$): δ 9.5, 16.1, 79.6; IR (neat): 1456 (w), 1401 (s), 1222 (w), 1187 (s), 957 (m), 828 (s), 778 (m), 592 (m) cm$^{-1}$; HRMS-(DART-TOF) for $C_5H_9O_4S$ [M+H]: calculated: 165.02215, found: 165.0223.



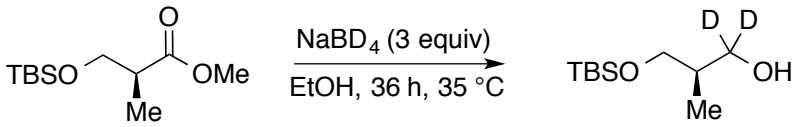
**(1-Benzylcyclopropyl)methyl hydrogen sulfate.** Prepared according to the general cross-coupling procedure with isolation of the sulfate half ester using (*R,R*)-PhenylPyBox (**L3**) as the ligand instead of **L5**. The crude reaction mixture was purified by silica gel chromatography (10% MeOH in ethyl acetate) to afford a white solid (48 mg, 56% yield). $R_f$ = 0.08 (10% MeOH in ethyl acetate, stain in CAM). $^1$H NMR (600 MHz, $CD_3OD$): δ 0.53 (4H, s), 2.73 (2H, s), 3.72 (2H, s), 7.17 (1H, m), 7.25 (4H, d, *J* = 6.0 Hz); $^{13}$C NMR (151 MHz, $CDCl_3$): δ 10.6, 22.0, 40.5, 74.6, 127.3, 129.3, 130.9, 140.8; IR (neat): 3408 (br), 3062 (w), 3027 (w), 3001 (w), 2502 (br), 1603 (w), 1204 (s), 1060 (s), 945 (s), 824 (m), 721 (m), 700 (m), 581 (s) cm$^{-1}$; HRMS-(DART-TOF) for $C_{11}H_{18}NO_4S$ [M+$NH_4$]: calculated: 260.09565, found: 260.09483.

*$^2$H-labeling Studies:*



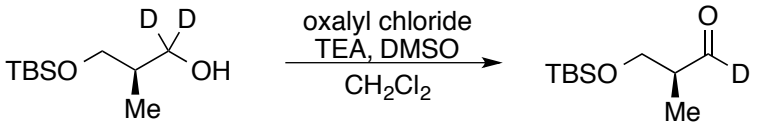

***Methyl (S)-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanoate*** was prepared according to the literature procedure from commercial *(S)*-roche ester as shown above.[140]

[140] Kalesse, M.; Chary, K. P.; Quitschalle, M.; Burzlaff, A.; Kasper, C.; Scheper, T. *Chem. Eur. J.* **2003**, *9*, 1129




**SI-9**

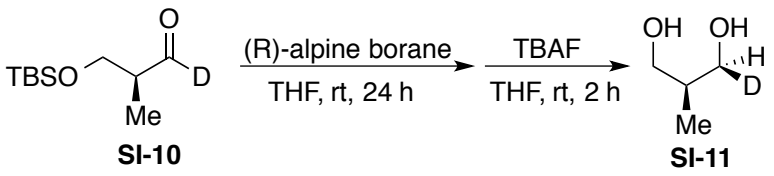
**(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropan-1,1-$d_2$-1-ol (SI-9)**. To an oven dried 50 mL round bottom flask containing a solution of methyl *(S)*-3-((tert-butyldimethylsilyl)oxy)-2-methylpropanoate (2.86 g, 12.3 mmol) in ethanol (25 mL) was added sodium borodeuteride (1.54 g, 36.9 mmol) as a solid in portions. The reaction was allowed to stir at 35 °C for 36 h before being cooled to room temperature and quenched with water. The mixture was diluted with ethyl acetate and organic layer washed with water and brine. The organic layer was then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (10:1 hexane: ethyl acetate) to provide the desired product as colorless oil (1.84 g, 73% yield). $R_f$ = 0.37 (5:1 hexane: ethyl acetate, stain in $KMnO_4$).$^1$H NMR (500 MHz, $CDCl_3$): δ 0.07 (6H, s), 0.84 (3H, d, *J* = 5.5 Hz), 0.90 (9H, s), 1.90- 1.94 (1H, m), 3.54 (1H, dd, *J* = 10.0 Hz, 8.0 Hz), 3.74 (1H, dd, *J* = 10.0 Hz, 4.5 Hz); $^{13}$C NMR (151 MHz, $CDCl_3$): δ -5.6, 13.0, 18.1, 25.8, 36.8, 67.3-67.7 (m), 68.6; IR (neat): 3365 (br, m), 2955 (m), 2929 (m), 2886 (m), 2857 (m), 1471 (m), 1082 (m), 835 (s) cm$^{-1}$; HRMS-(DART-TOF) for $C_{10}H_{23}D_2O_2Si$ [M+H]: calculated: 207.17493, found: 207.17601. $[\alpha]^{22}_D$ = 7.820 (c = 1.120, $CHCl_3$).




**SI-9** **SI-10**

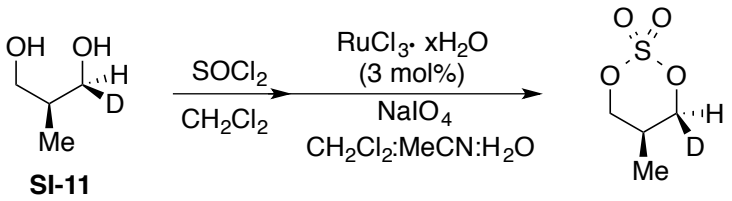
**(*S*)-3-((tert-Butyldimethylsilyl)oxy)-2-methylpropanal-1-*d* (SI-10)**. The title compound was prepared according to literature procedure with slight modification.[141] To a stirred solution of oxalyl chloride (0.29 mL, 3.35 mmol) in dichloromethane at -78 °C was added dimethyl sulfoxide (0.35 mL, 4.99 mmol) dropwise. The solution was allowed to stir for 10 minutes before **SI-9** (746 mg, 2.27 mmol) added slowly dropwise, followed by dropwise addition of triethylamine (1.60 mL, 11.35 mmol). The solution was then allowed to stir at -78 °C for 2 hours before warming to 0 °C and quenching with water. The mixture was then extracted with diethyl ether. The organic layer was washed with water and brine, then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (20:1 hexane: ethyl acetate) to provide the desired product as a light yellow oil (653 mg, 88% yield). $R_f$ = 0.17 (30:1 hexane: ethyl acetate, stain in $KMnO_4$). $^1$H NMR (500 MHz, $CDCl_3$): δ 0.05 (6H, s), 0.87 (9H, s), 1.08 (3H, d, *J* = 6.5 Hz), 2.52 (1H, m), 3.80 (1H, dd, *J* = 10.0 Hz, 7.0 Hz), 3.85 (1H, dd, *J* = 10.0 Hz, 5.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ – 5.5, 10.2, 18.2, 25.7, 48.6, 63.4, 204.4 (t, *J* = 26.4 Hz); IR (neat): 2954 (m), 2930 (m), 2886 (w), 2857 (m), 1719 (m), 1471 (w), 1255 (m), 835 (s) cm$^{-1}$; HRMS-(DART-TOF) for $C_{10}H_{22}DO_2Si$ [M+H]: calculated: 204.15301, found: 204.15401. $[\alpha]^{22}_D$ = 26.720 (c = 0.925, $CHCl_3$).

[141] Van Devender, E. A.; Marshall, J. A. *J. Org. Chem.* **2001**, *66*, 8037



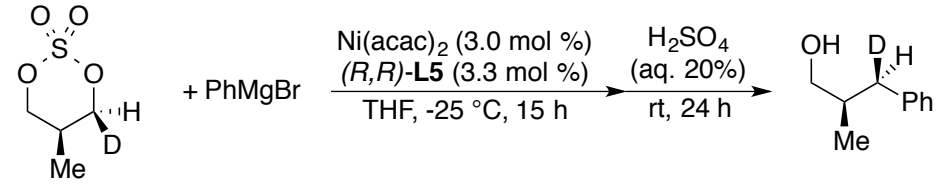

**SI-10** **SI-11**

**(1*S*,2*S*)-2-Methylpropane-1-*d*-1,3-diol (SI-11)**. To an oven dried 10 mL round bottom flask with magnetic stir bar was added **SI-10** (539 mg, 1.64 mmol) followed by THF (1.0 mL) and cooled to – 78 °C before *(R)*-alpine borane (0.5 M in THF, 6.6 mL, 3.29 mmol) added dropwise. The solution was allowed to warm to room temperature and stir for 24 h before quenching with saturated ammonium chloride. The solution was then extracted with dichloromethane (5 mL x 3). The organic layers were combined dried over anhydrous sodium sulfate, filtered and concentrated by rotary evaporation. The crude material was then dissolved in THF (2.2 mL) and tetrabutylammonium fluoride (1.0 M in THF, 2.5 mL, 2.5 mmol) added. The solution was then allowed to stir for 2 h at room temperature before concentrating under reduced pressure. The crude product was purified by silica gel chromatography (1:1 diethyl ether: ethyl acetate) to yield the title compound as a colorless oil (72 mg, 48% yield). $R_f$ = 0.28 (2:1 diethyl ether: ethyl acetate, stain in $KMnO_4$).$^1$H NMR (500 MHz, $CDCl_3$): δ 0.85 (3H, d, *J* = 6.6 Hz), 1.91- 1.94 (1H, m), 2.92 (2H, brs), 3.58 (1H, dd, *J* = 9.6 Hz, 7.2 Hz), 3.68- 3.71 (3H, m); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 13.0, 37.0, 67.3 (t, *J* = 20.8 Hz), 67.7; IR (neat): 3329 (br, m), 2959 (m), 2927 (m), 1381 (m), 1457 (m), 1030 (s) cm$^{-1}$; HRMS-(DART-TOF) for $C_4H_{10}DO_2$ [M+H]: calculated: 92.08218, found: 92.08231.




**SI-11**

**(4*S*,5*S*)-5-Methyl-1,3,2-dioxathiane 2,2-dioxide-4-*d*.** The title compound was prepared according to the general procedure with **SI-11** (72 mg, 0.78 mmol). The crude reaction mixture was purified by silica gel chromatography (4:1 pentane: diethyl ether to 100% diethyl ether) to afford a white solid (57.0 mg, 48% yield). $R_f$ = 0.33 (3:1 pentane: diethyl ether, stain in $KMnO_4$). $^1$H NMR (500 MHz, $CDCl_3$): δ 1.05 (3H, d, *J* = 6.5 Hz), 2.40- 2.46 (1H, m), 4.44 (1H, dd, *J* = 11.0 Hz, 9.0 Hz), 4.56- 4.60 (2H, m); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 11.2, 27.9, 77.4 (t, *J* = 22.75 Hz), 77.7; IR (neat) 2954 (m), 2919 (m), 2344 (m), 1386 (s), 1157 (s), 908 (m), 834 (m), 440 (m) $cm^{-1}$; HRMS-(DART-TOF) for $C_4H_8DO_4S$ [M+H]: calculated: 154.02843 found: 154.02887.

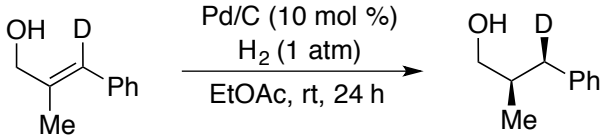



**(2*R*,3*R*)-2-Methyl-3-phenylpropan-3-*d*-1-ol.** Prepared according to the general cross-coupling procedure with **23** (0.30 mmol) and phenylmagnesium bromide. The crude reaction mixture was purified by silica gel chromatography (4:1 pentane: diethyl ether) to afford a colorless oil (47.2 mg, 81% yield). $R_f$ = 0.14 (3:1 pentane: diethyl ether, stain in

PMA). $^{1}$H NMR (600 MHz, $CDCl_3$): δ 0.92 (3H, d, *J* = 6.6 Hz), 1.31 (1H, brs), 1.94 (1H, hept, *J* = 6.6 Hz), 2.73 (1H, d, *J* = 6.6 Hz), 3.48 (1H, dt, *J* = 10.8 Hz, 5.4 Hz), 3.54 (1H, dt, *J* = 10.2 Hz, 4.8 Hz), 7.17- 7.20 (3H, m), 7.28 (2H, t, J= 7.8 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 16.4, 37.7, 39.3 (t, *J* = 19.8 Hz), 67.7, 125.8, 128.2, 129.1, 140.6; IR (neat): 3337 (br), 3083 (w), 3061 (w), 2955 (m), 2872 (m), 1377 (w), 1227 (m), 734 (m), 698 (s) $cm^{-1}$; HRMS-(DART-TOF) for $C_{10}H_{14}DO$ [M+H]: calculated: 152.11857, found: 152.11791.

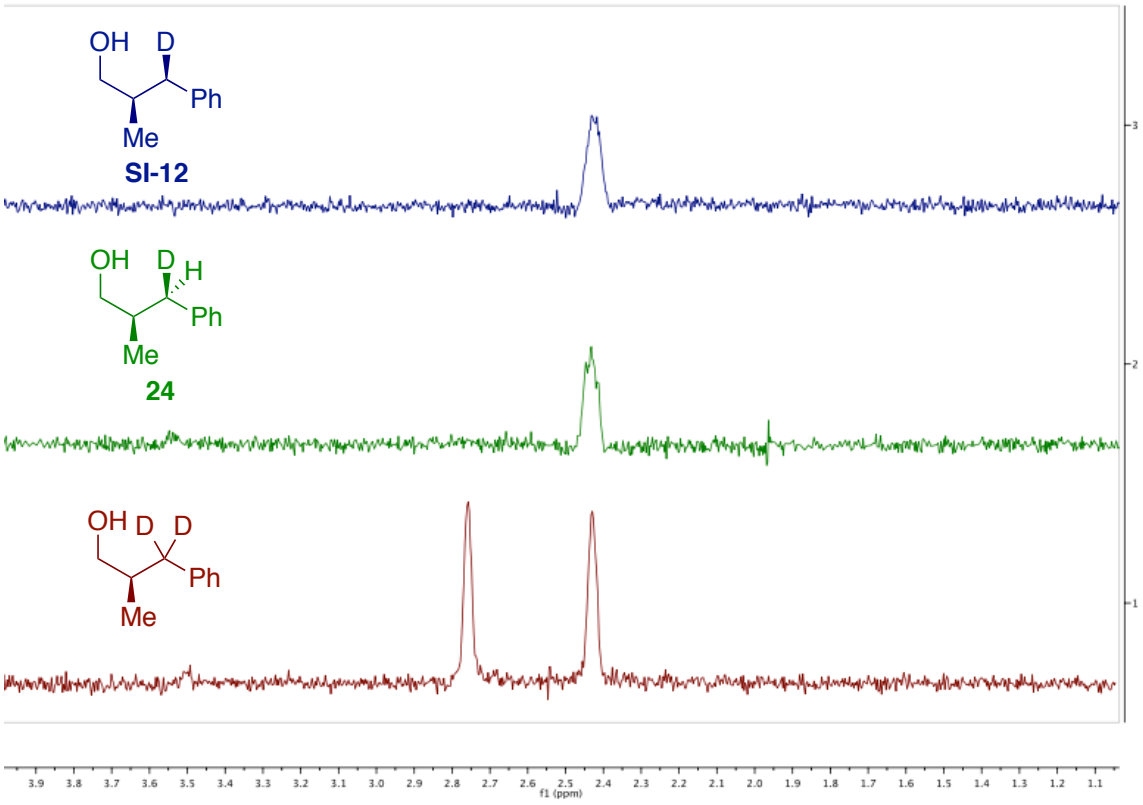
*Proof of Configuration:*

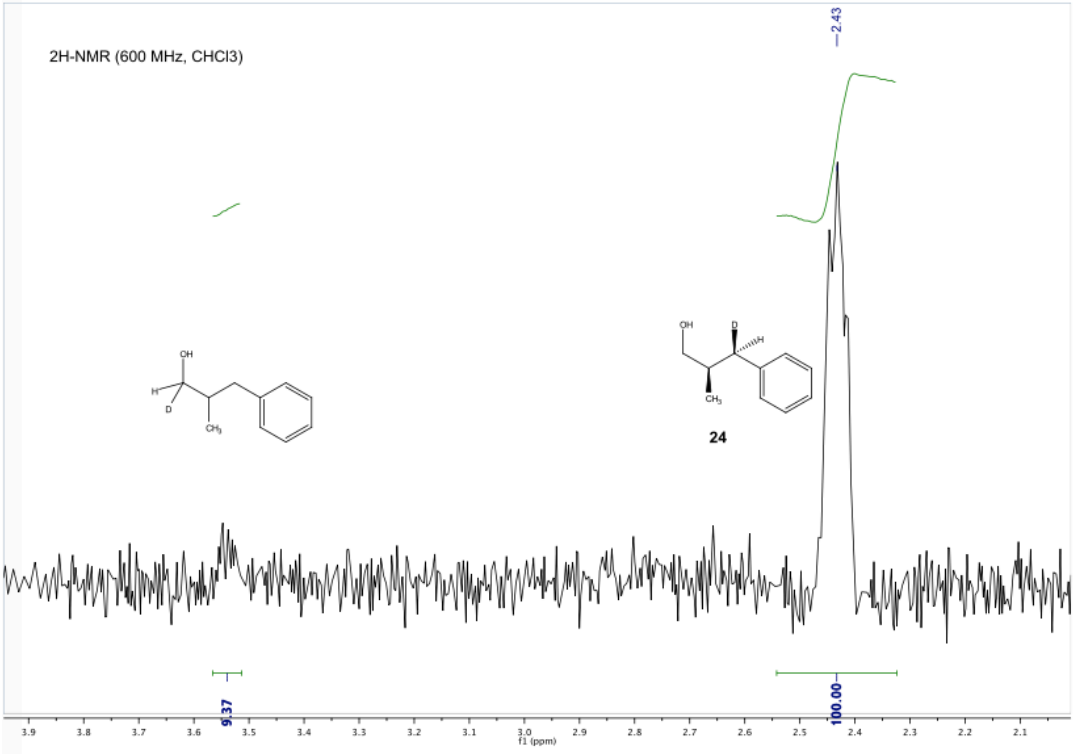
The configuration of **27** was determined by comparison with racemic product, synthesized by hydrogenation of the corresponding deuterium labeled allylic alcohol.



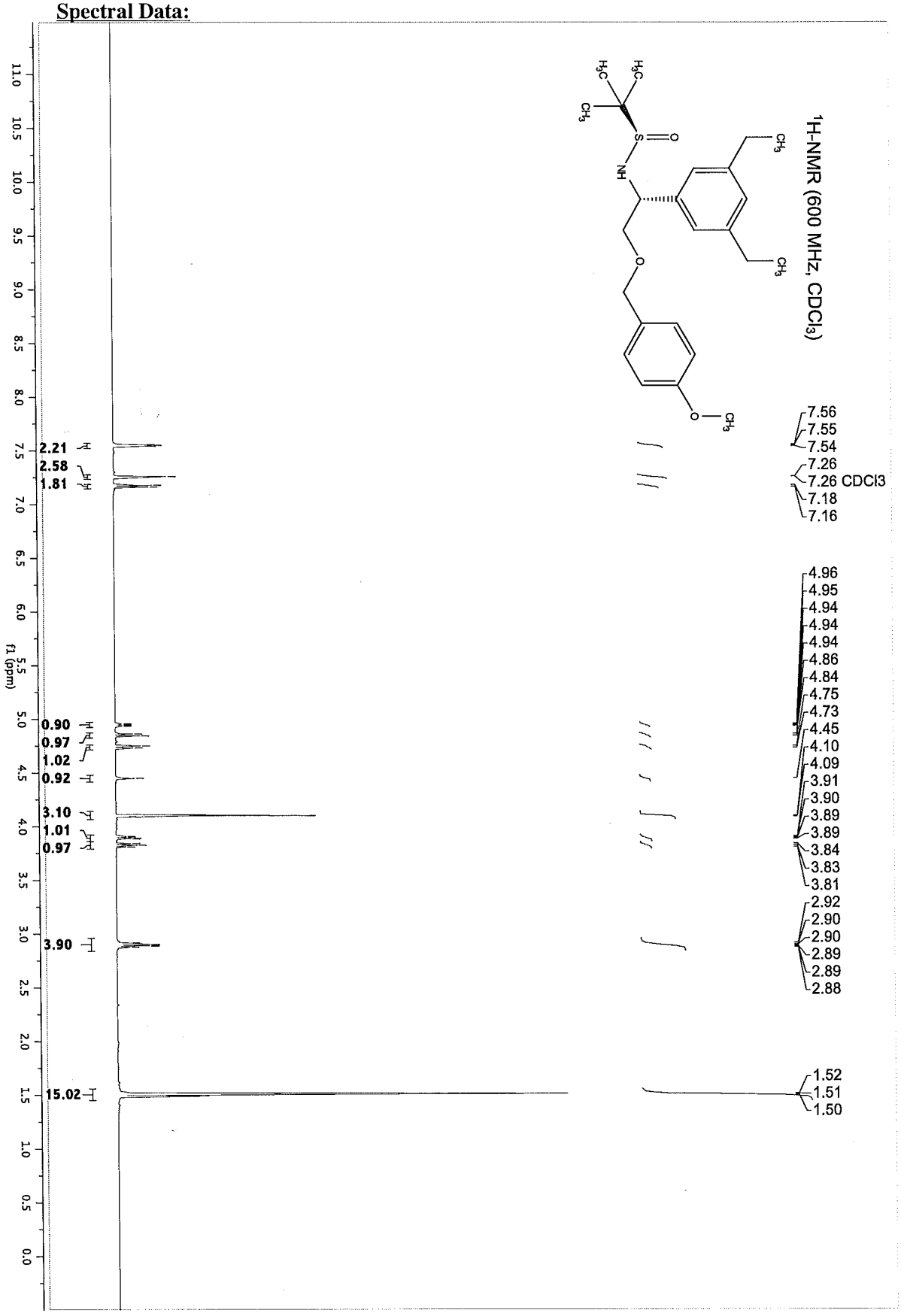

**SI-12**

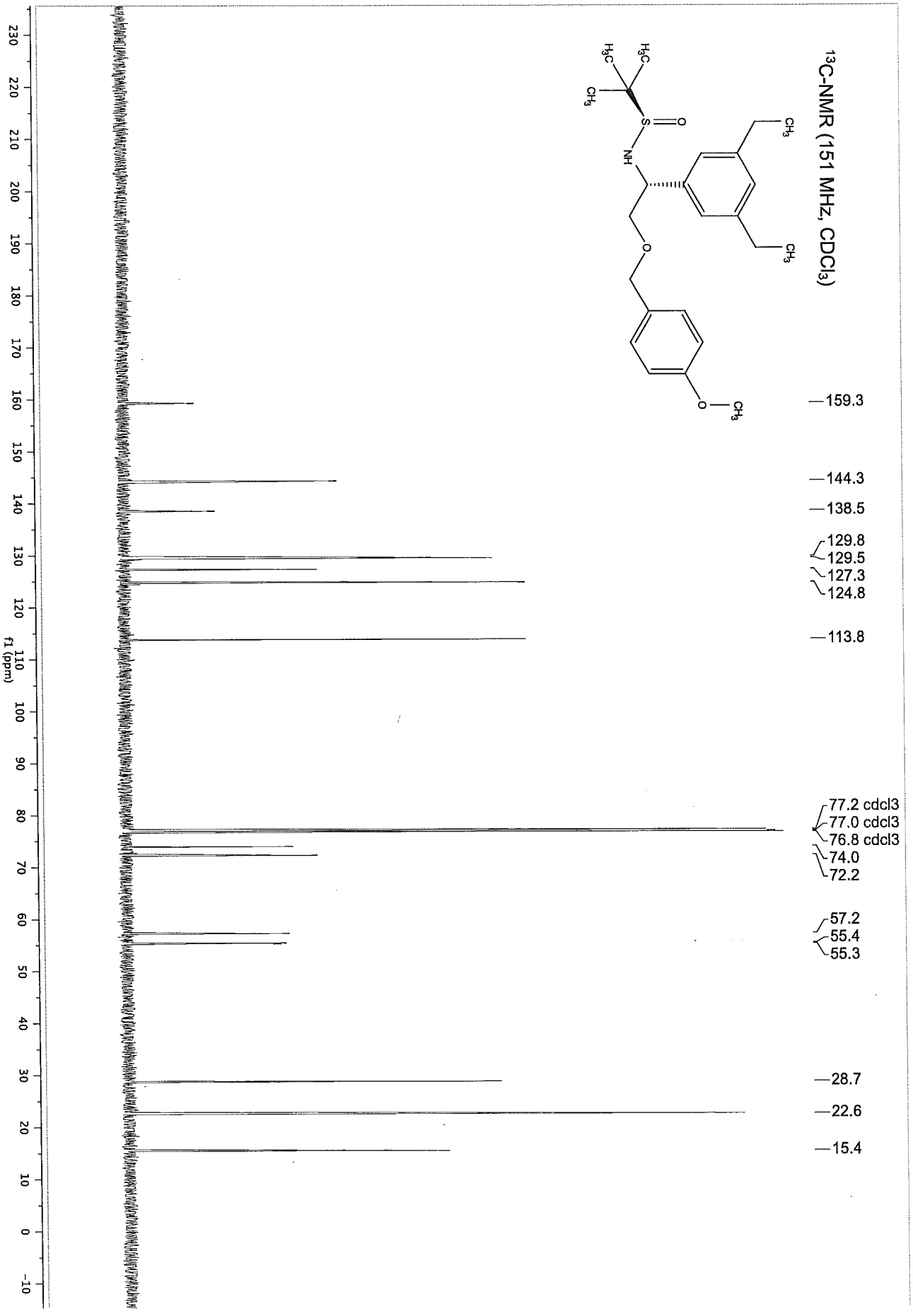
## $^{2}$H-Labeling Experiments- $^{2}$H-NMR Spectra:

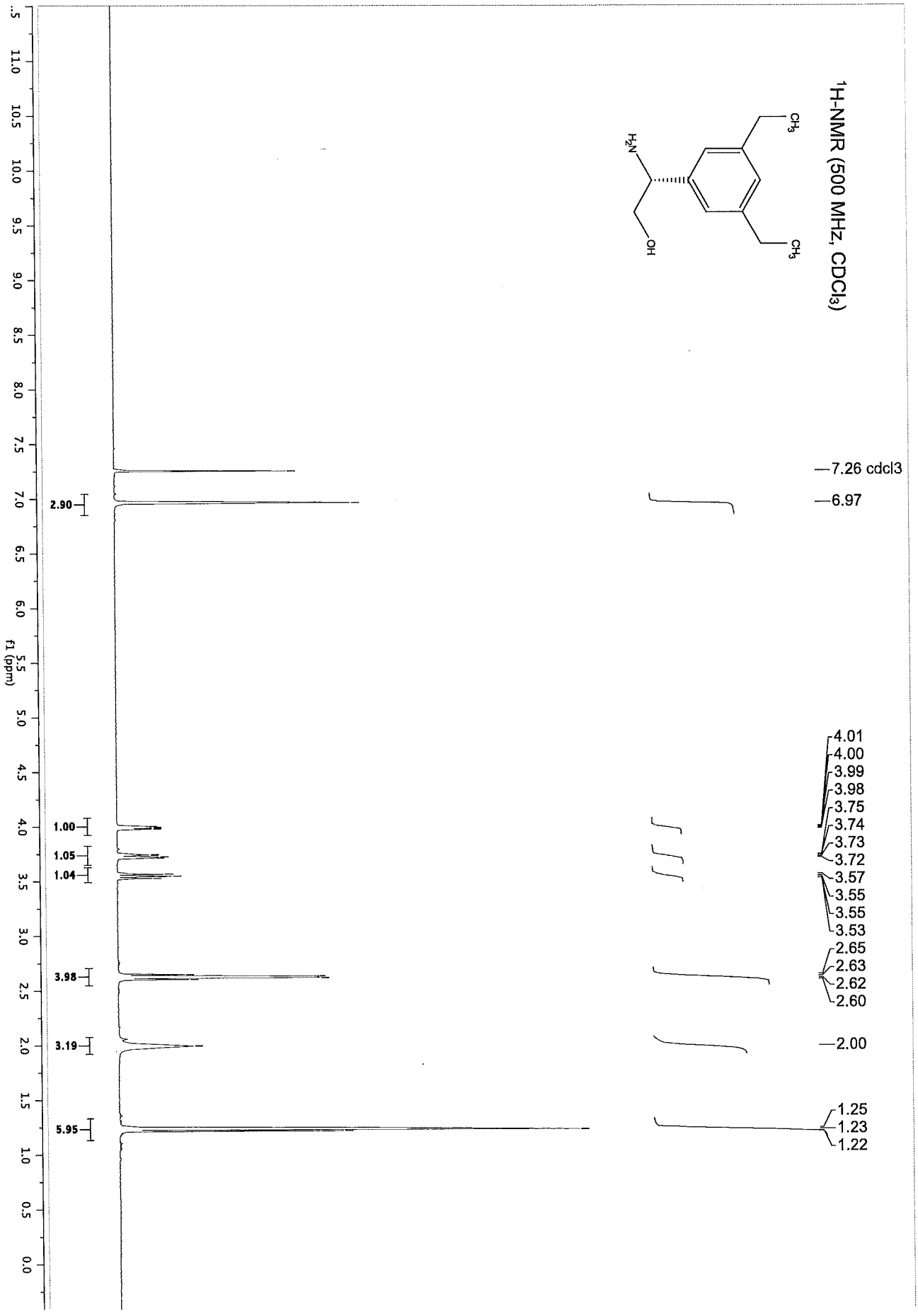


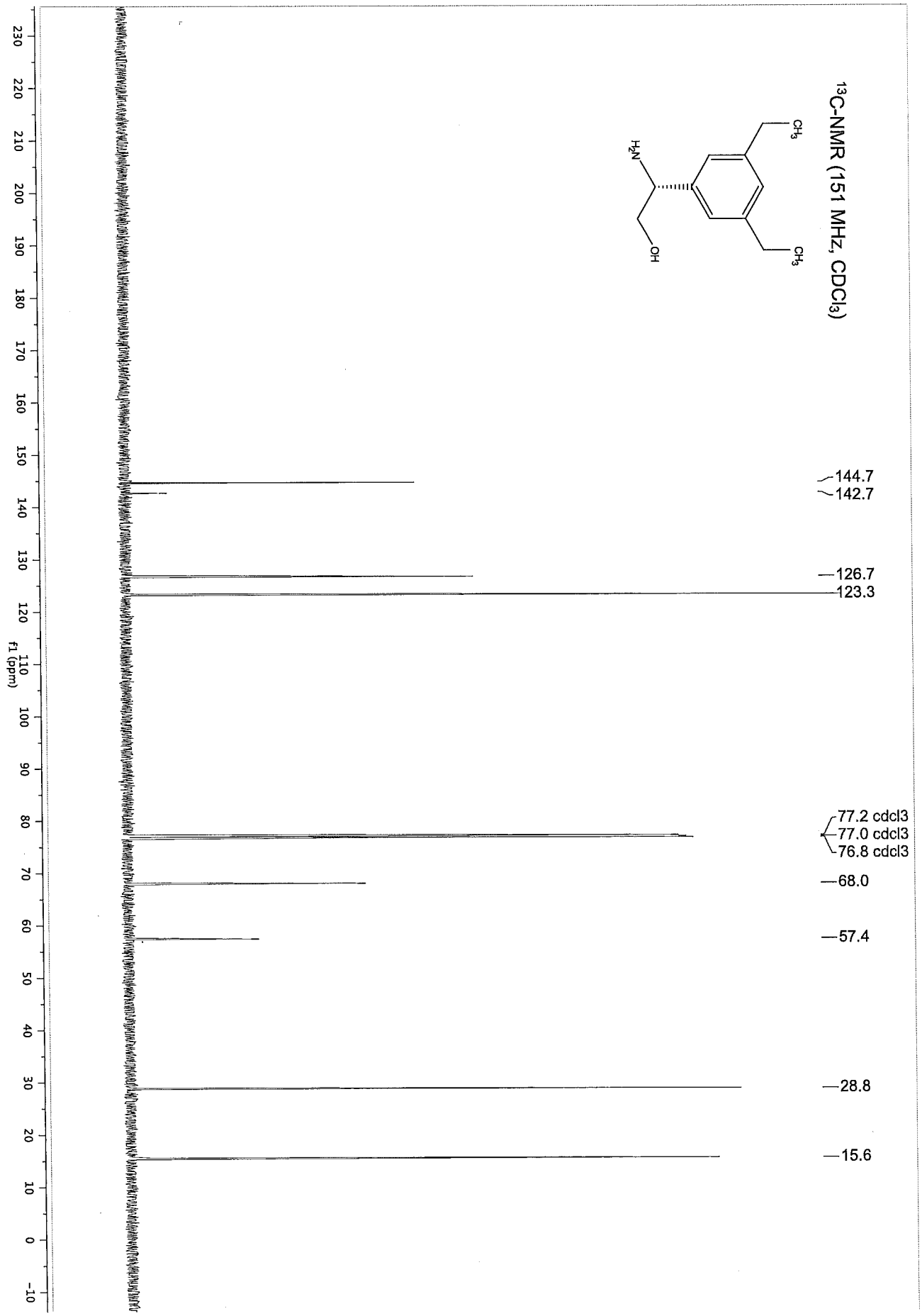



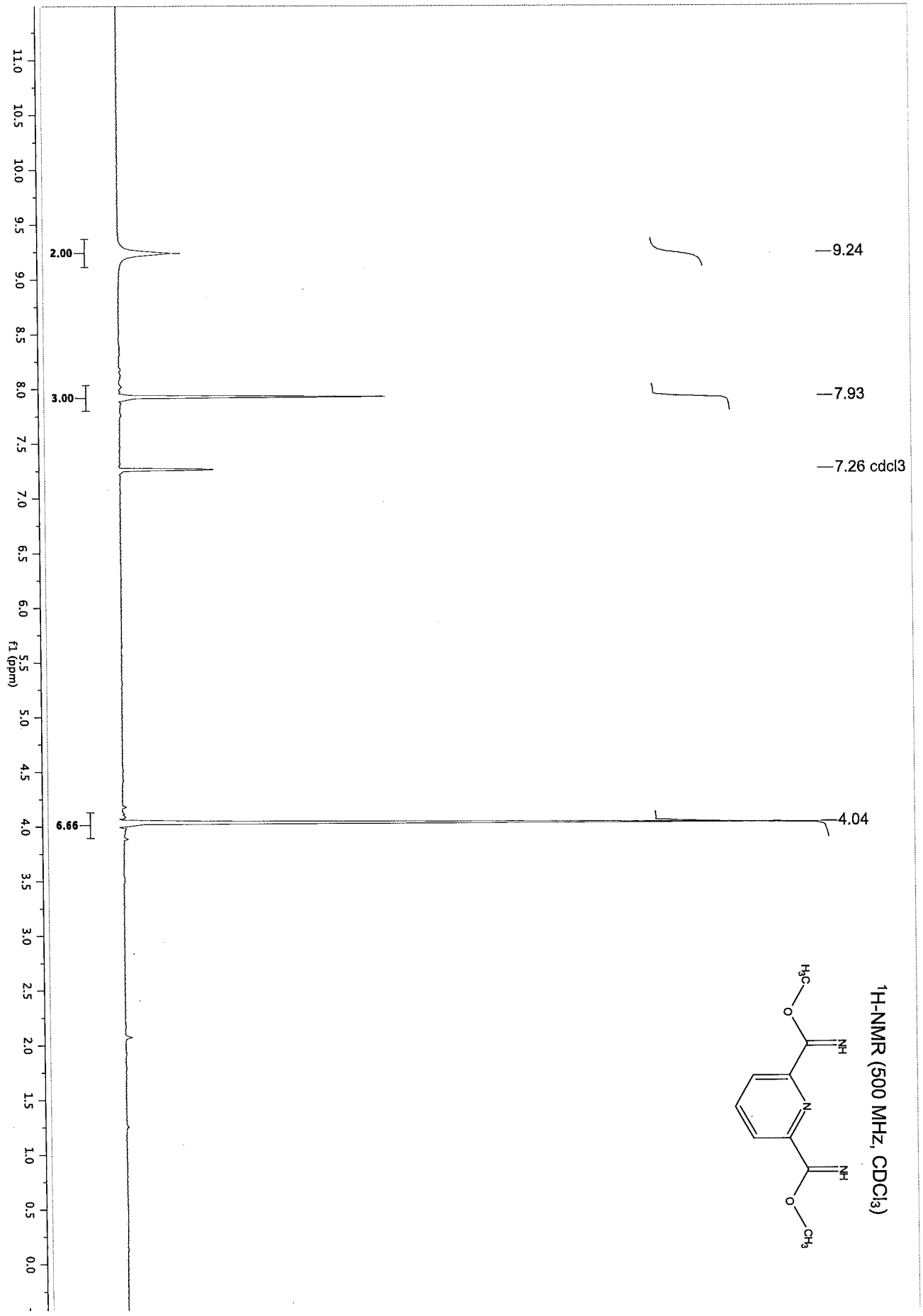
**Spectral Data:**



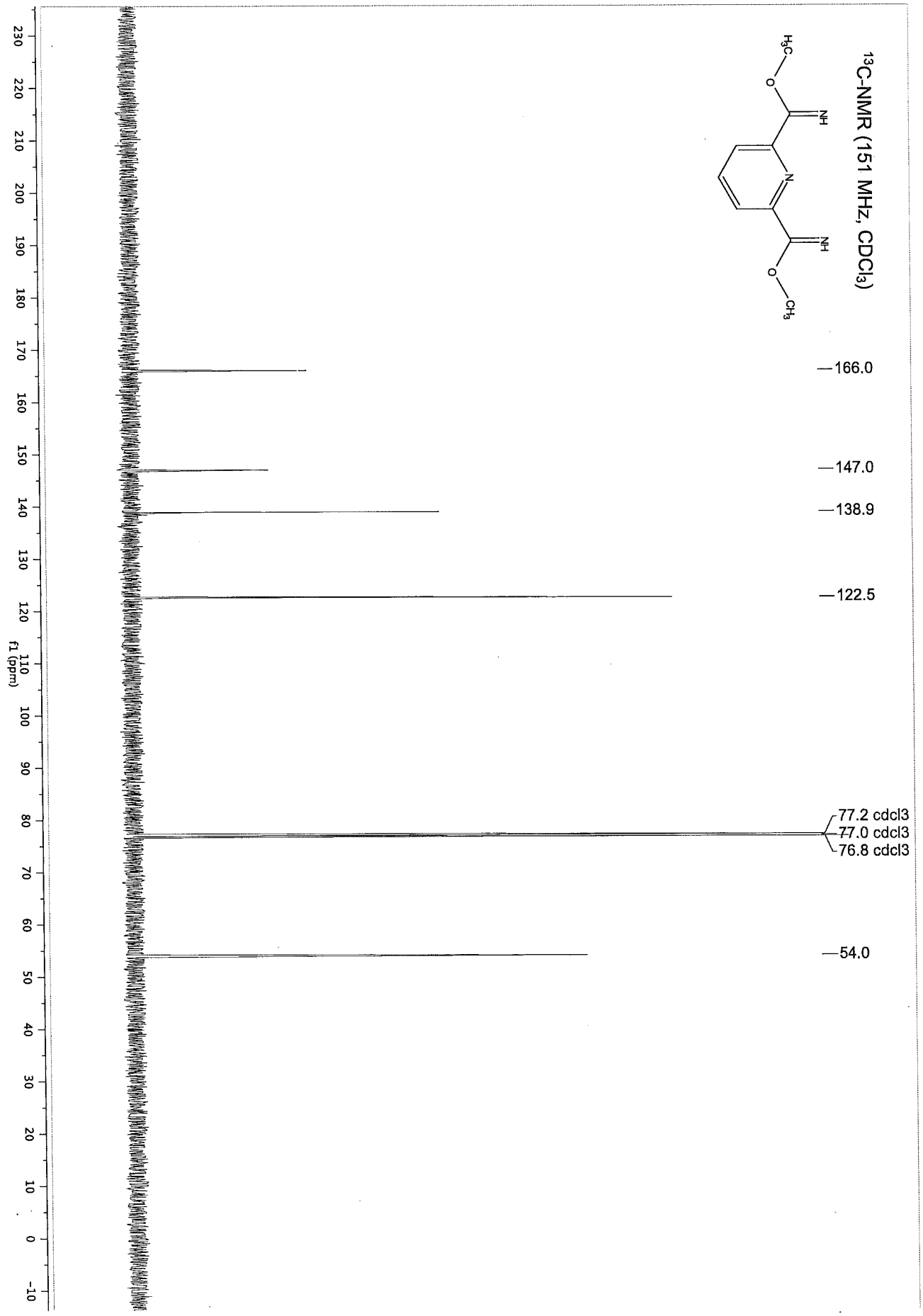

13C-NMR (151 MHz, CDCl3)
159.3
144.3
138.5
129.8
129.5
127.3
124.8
113.8
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
74.0
72.2
57.2
55.4
55.3
28.7
22.6
15.4
f1 (ppm)

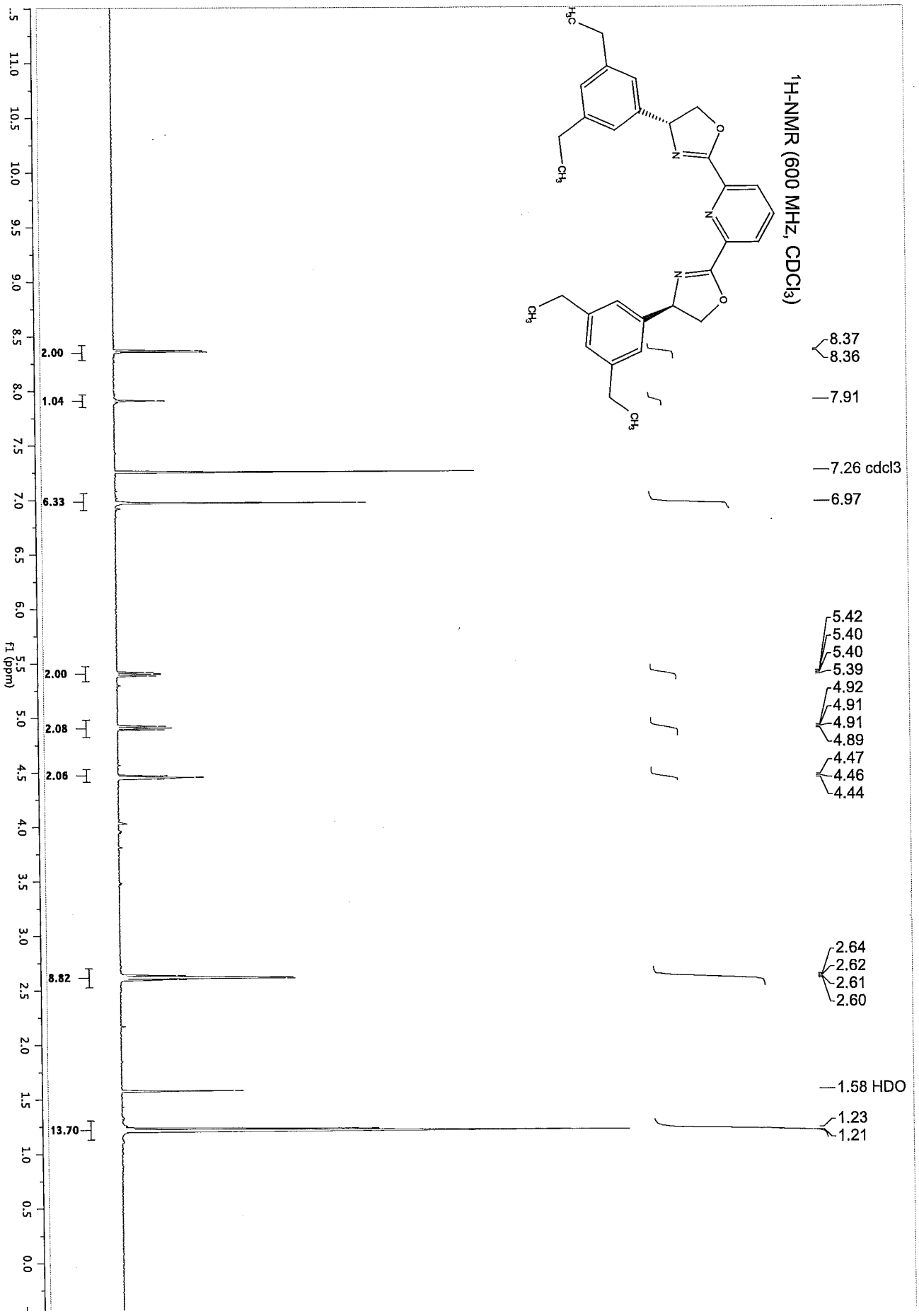

$^1$H-NMR (500 MHz, CDCl$_3$)
$H_2N$
OH
$CH_3$
$CH_3$
f1 (ppm)
2.90
1.00
1.05
1.04
3.98
3.19
5.95
—7.26 cdcl3
—6.97
4.01
4.00
3.99
3.98
3.75
3.74
3.73
3.72
3.57
3.55
3.55
3.53
2.65
2.63
2.62
2.60
—2.00
1.25
1.23
1.22

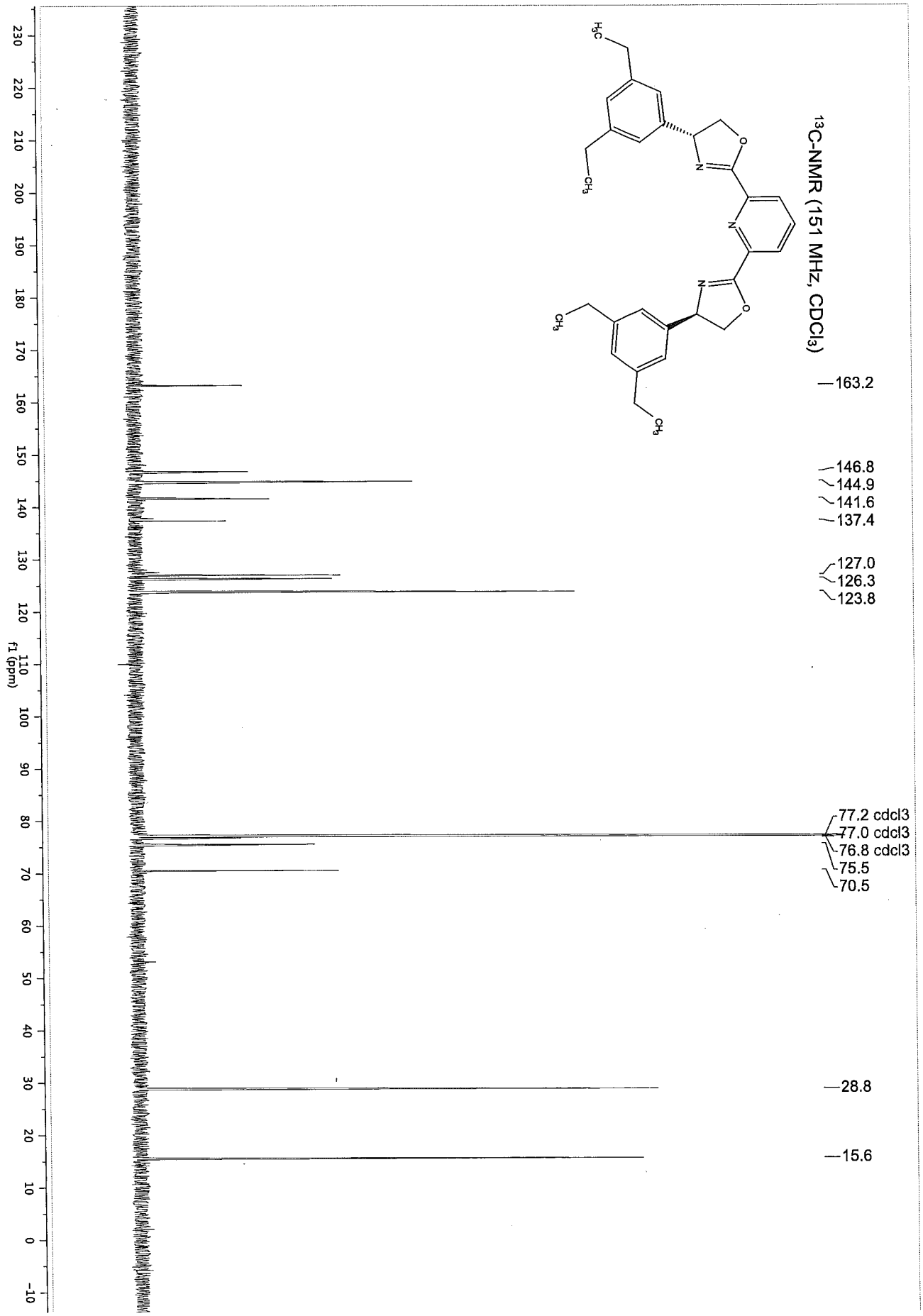

13C-NMR (151 MHz, CDCl3)
H2N
OH
CH3
CH3
144.7
142.7
126.7
123.3
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
68.0
57.4
28.8
15.6
f1 (ppm)

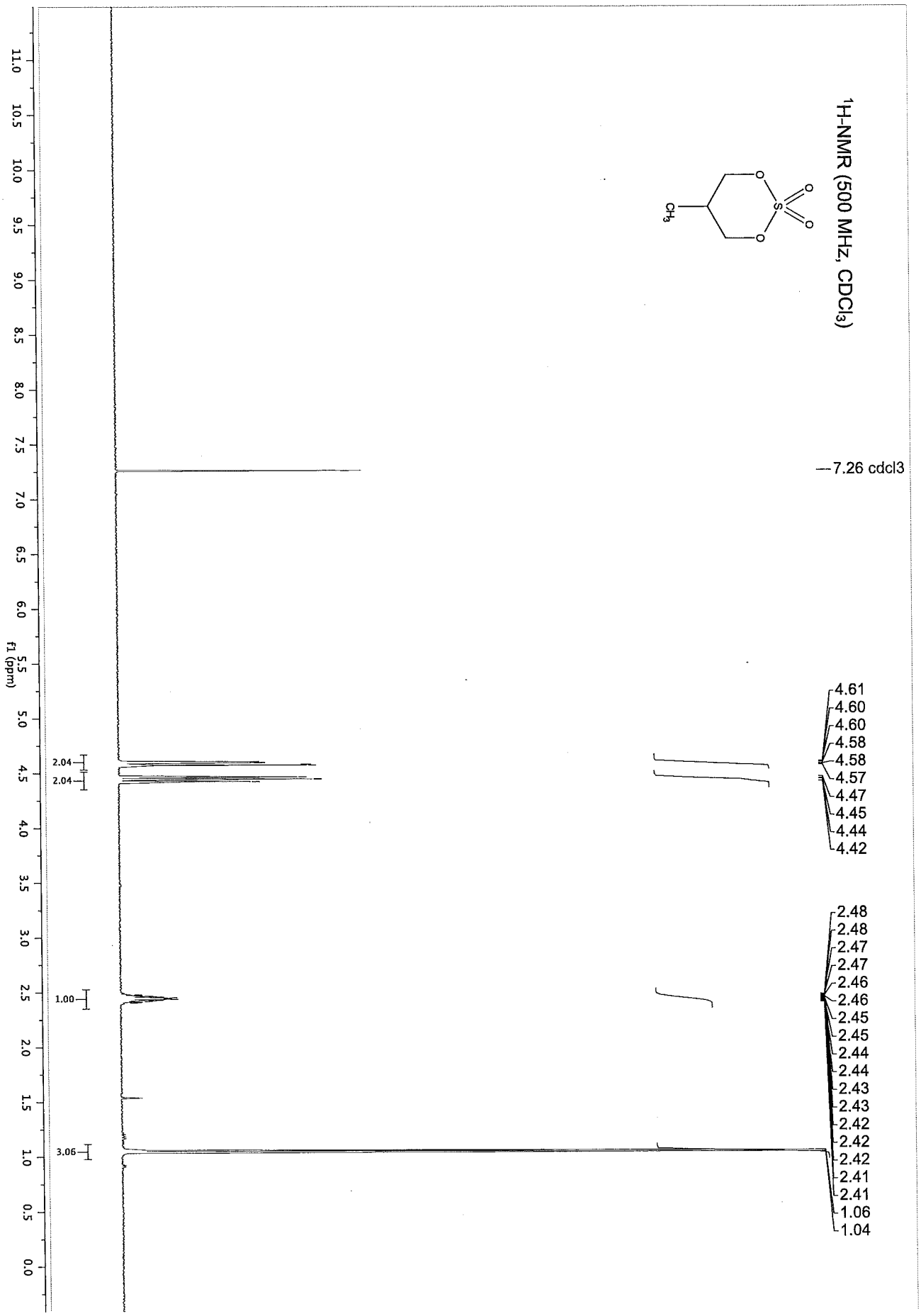


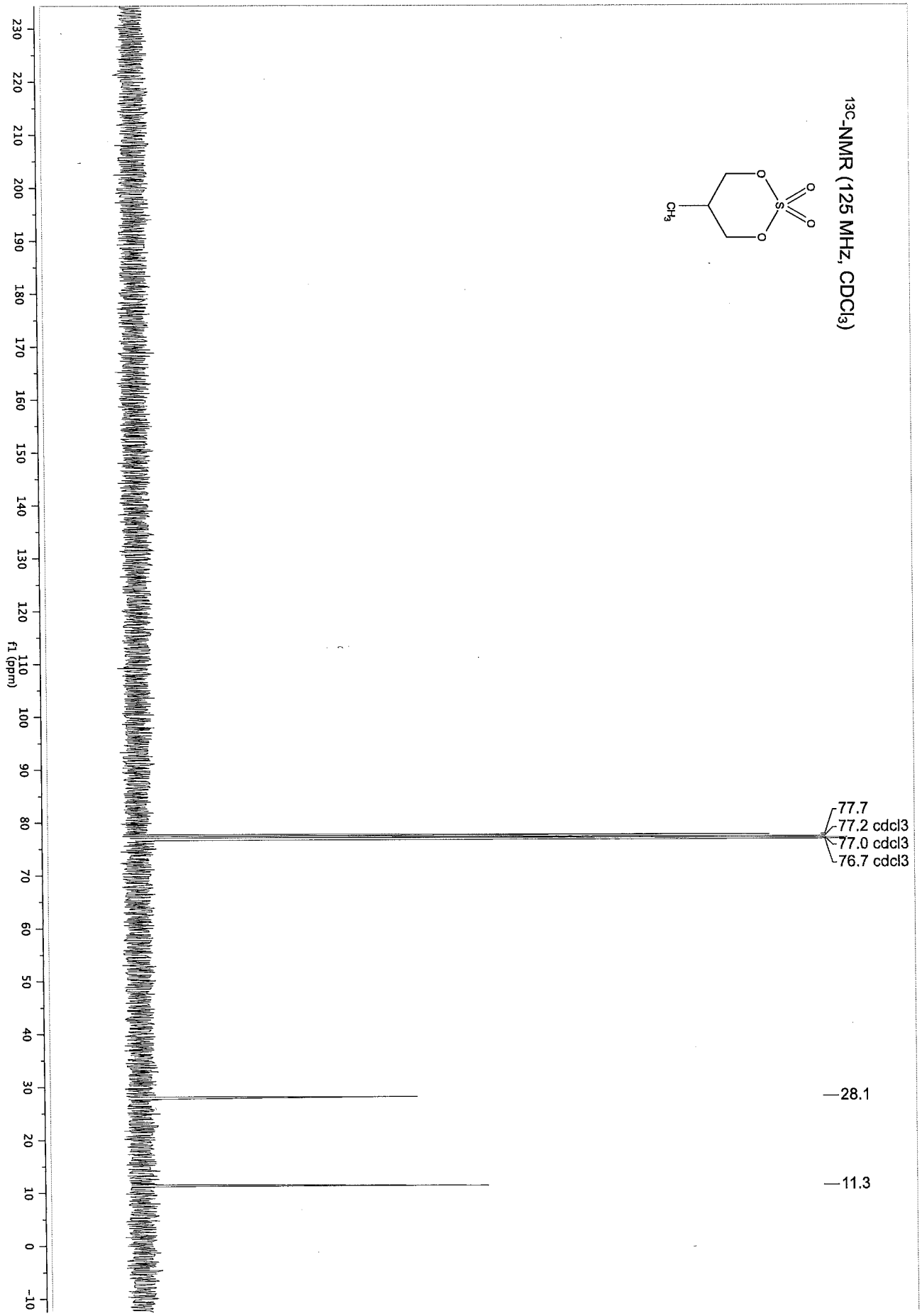

$^1$H-NMR (500 MHz, $CDCl_3$)

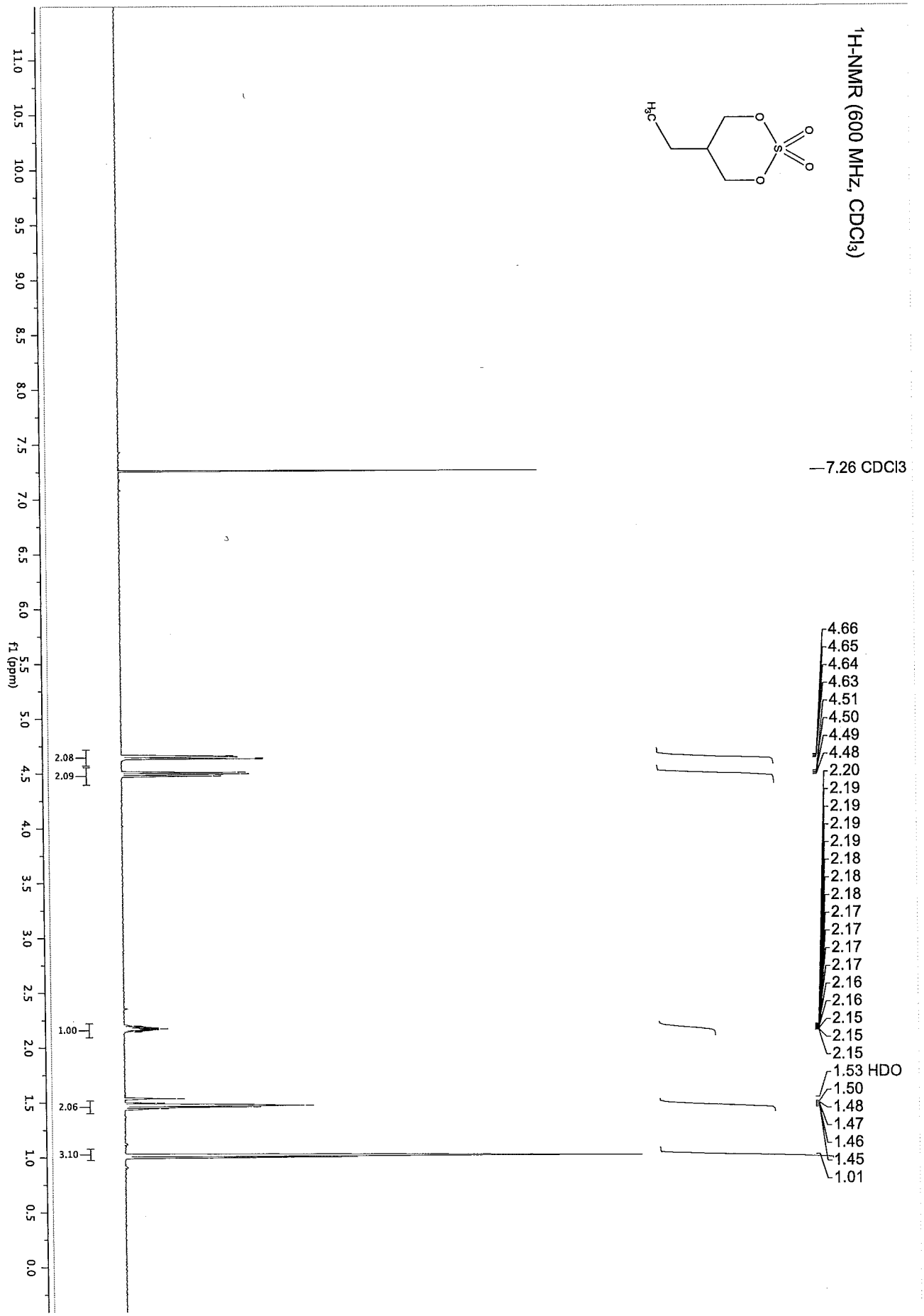

$^{13}$C-NMR (151 MHz, CDCl$_3$)
H$_3$C
O
NH
N
NH
O
CH$_3$
166.0
147.0
138.9
122.5
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
54.0
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

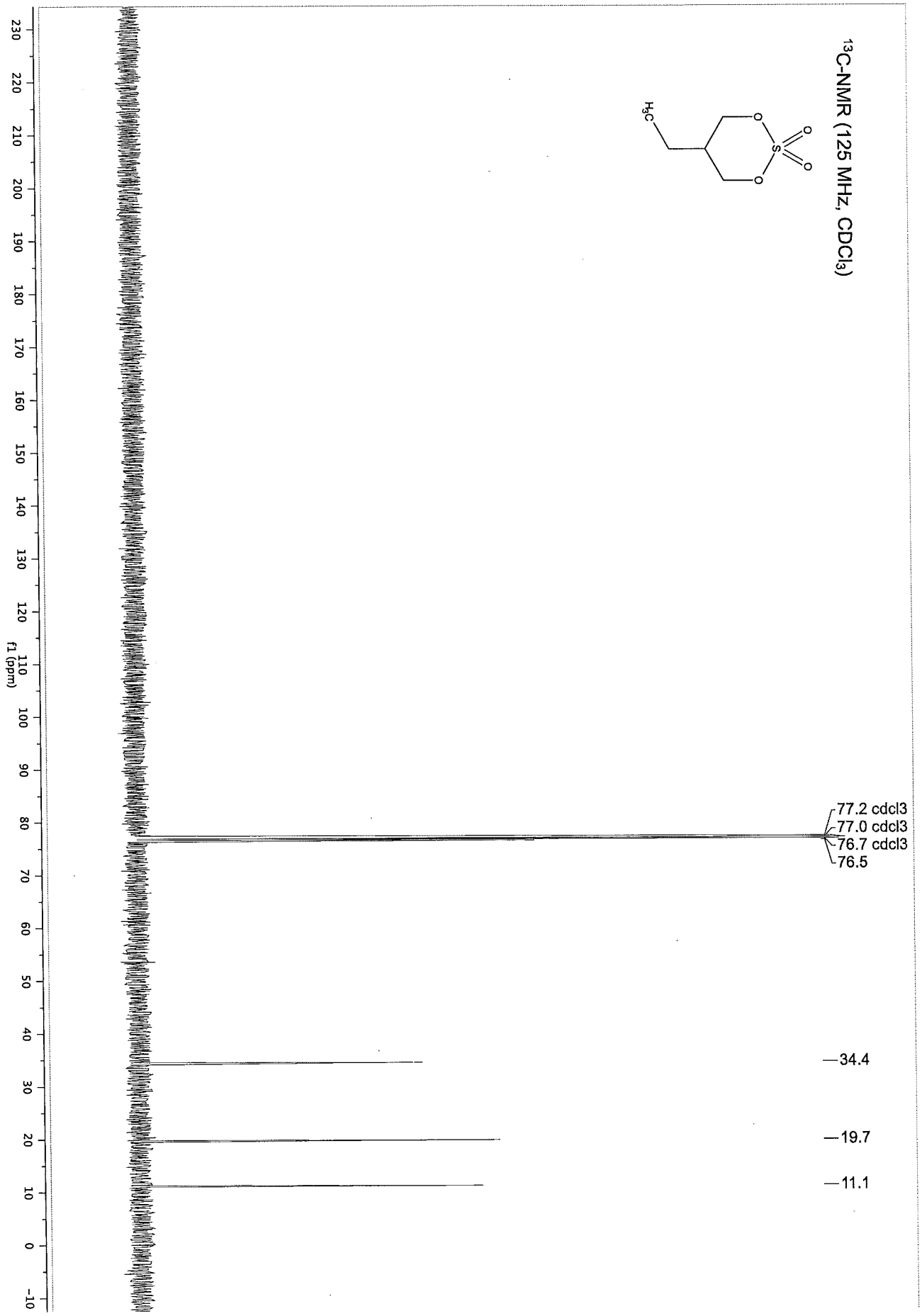

$^1$H-NMR (600 MHz, CDCl$_3$)
f1 (ppm)
2.00
1.04
6.33
2.00
2.08
2.06
8.82
13.70
8.37
8.36
7.91
7.26 cdcl3
6.97
5.42
5.40
5.40
5.39
4.92
4.91
4.91
4.89
4.47
4.46
4.44
2.64
2.62
2.61
2.60
1.58 HDO
1.23
1.21

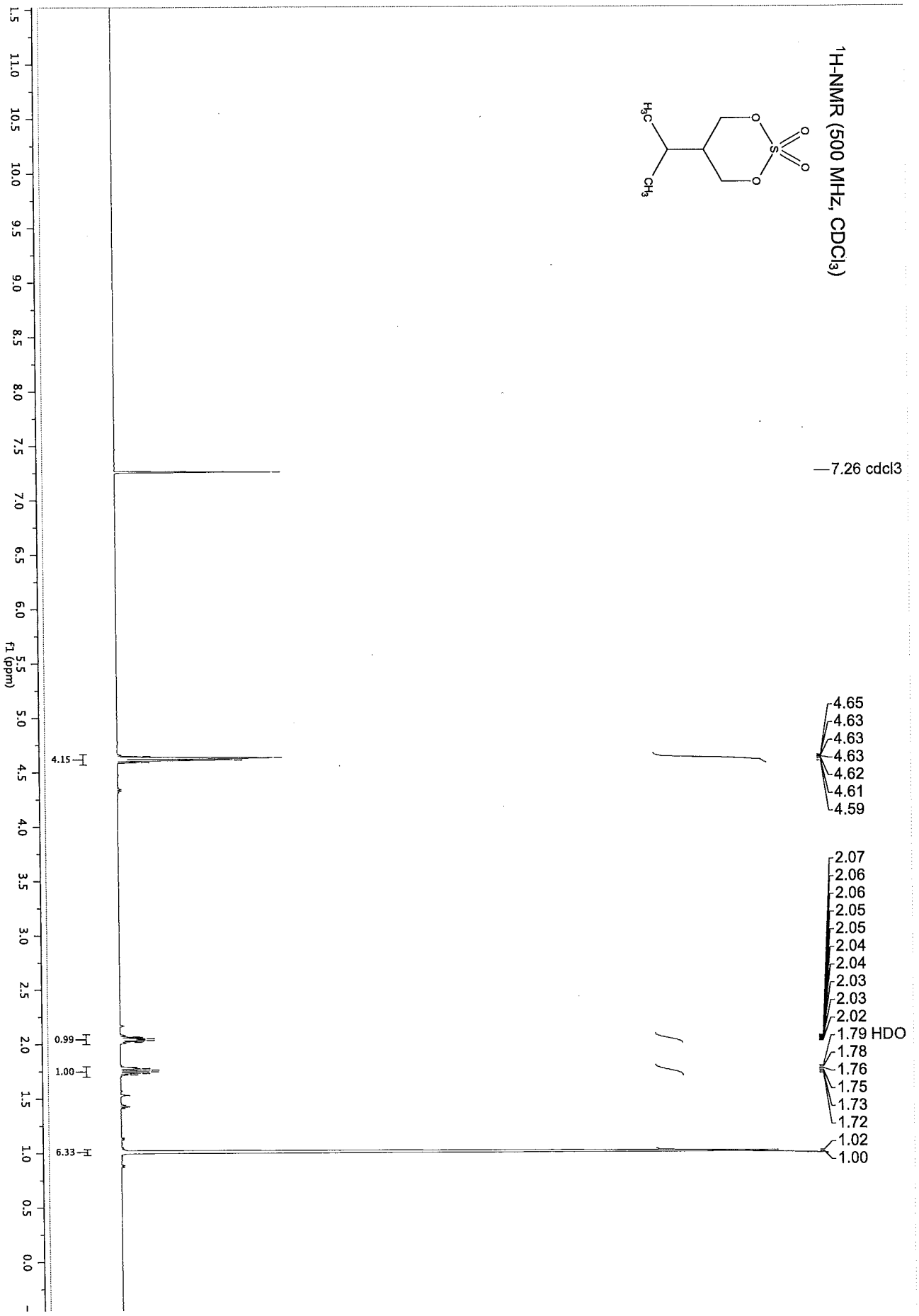

$^{13}$C-NMR (151 MHz, CDCl$_3$)
163.2
146.8
144.9
141.6
137.4
127.0
126.3
123.8
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
75.5
70.5
28.8
15.6
f1 (ppm)


$^1$H-NMR (500 MHz, CDCl$_3$)
CH$_3$
O
S
O
O
O
7.26 cdcl3
4.61
4.60
4.60
4.58
4.58
4.57
4.47
4.45
4.44
4.42
2.48
2.48
2.47
2.47
2.46
2.46
2.45
2.45
2.44
2.44
2.43
2.43
2.42
2.42
2.42
2.41
2.41
1.06
1.04
2.04
2.04
1.00
3.06
f1 (ppm)
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


13C-NMR (125 MHz, CDCl3)
CH3
77.7
77.2 cdcl3
77.0 cdcl3
76.7 cdcl3
28.1
11.3
f1 (ppm)


$^1$H-NMR (600 MHz, CDCl$_3$)
—7.26 CDCl3
4.66
4.65
4.64
4.63
4.51
4.50
4.49
4.48
2.20
2.19
2.19
2.19
2.19
2.18
2.18
2.18
2.17
2.17
2.17
2.17
2.16
2.16
2.15
2.15
2.15
1.53 HDO
1.50
1.48
1.47
1.46
1.45
1.01
2.08
2.09
1.00
2.06
3.10
f1 (ppm)


$^{13}$C-NMR (125 MHz, CDCl$_3$)
H$_3$C
O
S
O
O
O
77.2 cdcl3
77.0 cdcl3
76.7 cdcl3
76.5
34.4
19.7
11.1
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


$^1$H-NMR (500 MHz, CDCl$_3$)
H$_3$C
CH$_3$
O
S
O
O
O
f1 (ppm)
—7.26 cdcl3
4.65
4.63
4.63
4.63
4.62
4.61
4.59
2.07
2.06
2.06
2.05
2.05
2.04
2.04
2.03
2.03
2.02
1.79 HDO
1.78
1.76
1.75
1.73
1.72
1.02
1.00
4.15
0.99
1.00
6.33

$^{13}$C-NMR (125 MHz, $CDCl_3$)



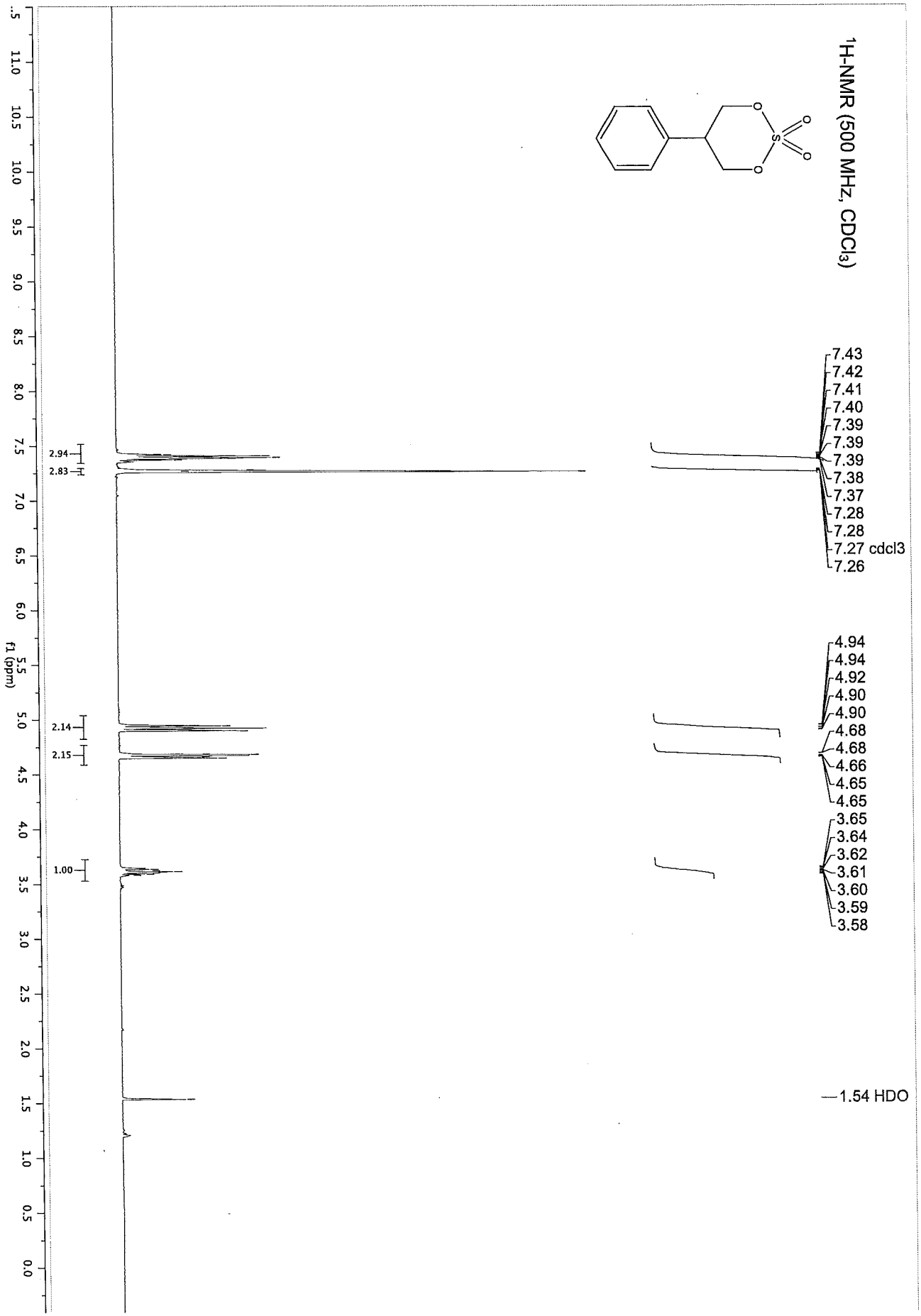

77.2 cdcl3
77.0 cdcl3
76.7 cdcl3
75.7

—38.9

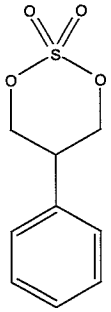
—26.0

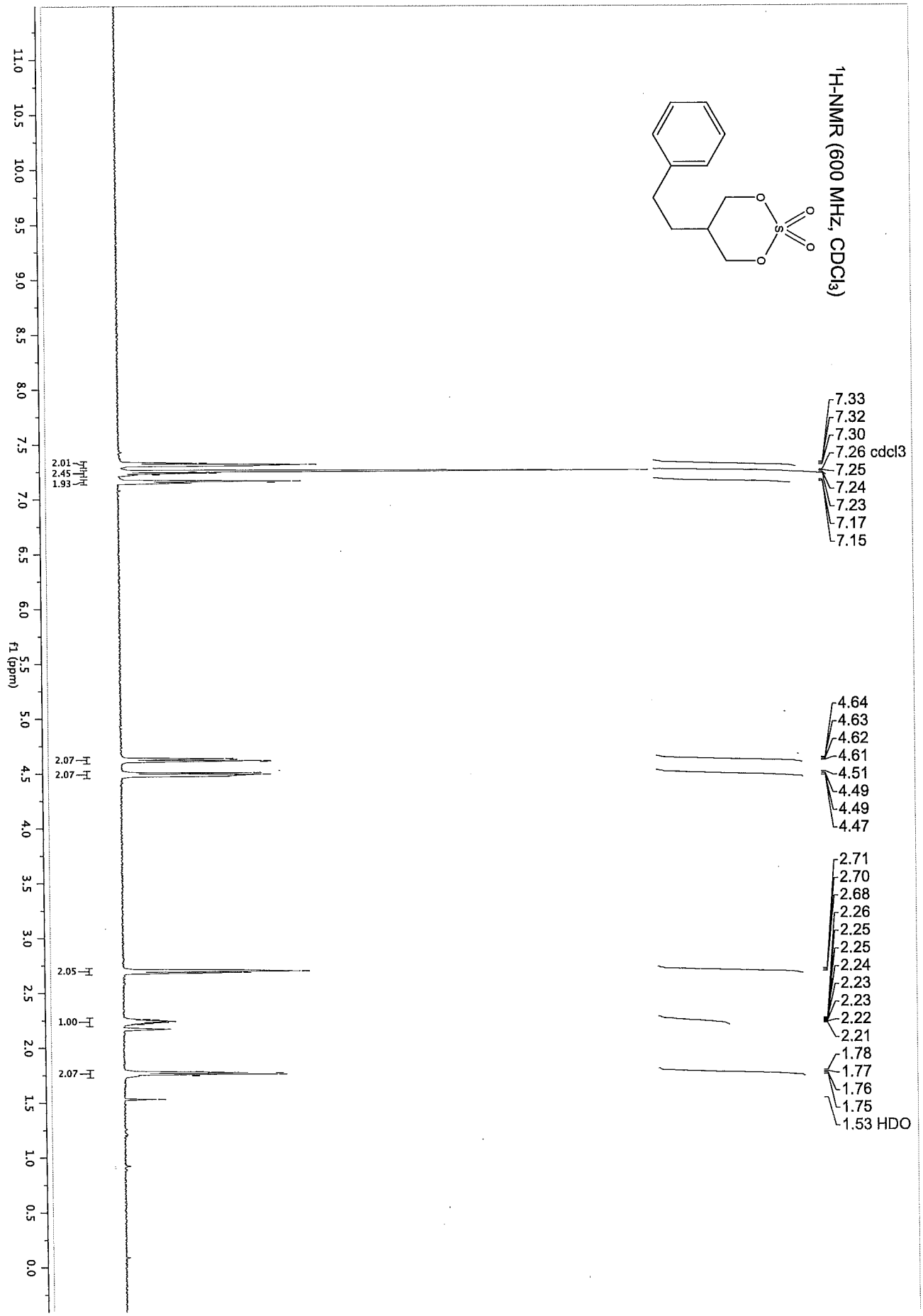
—20.1

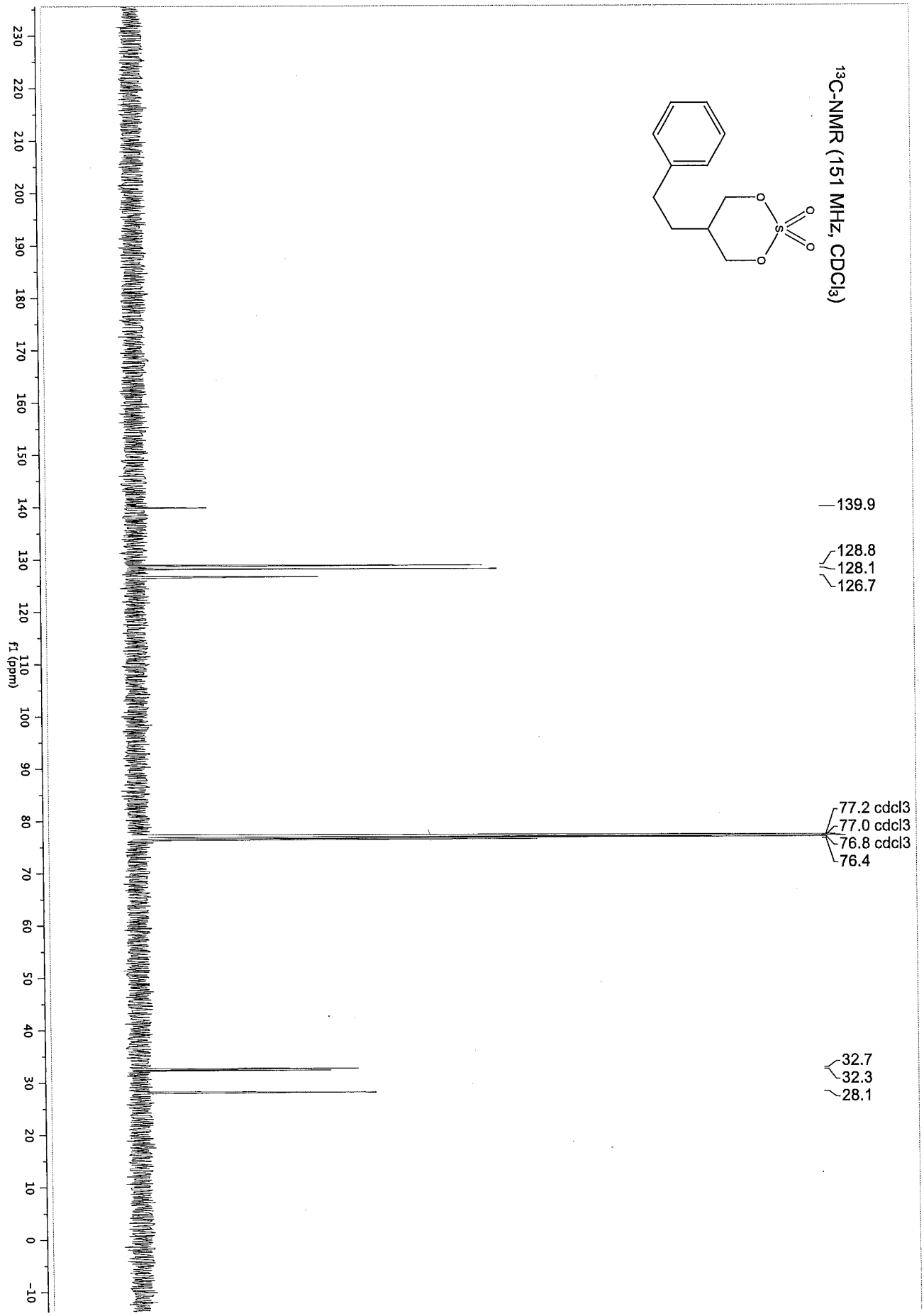
f1 (ppm)

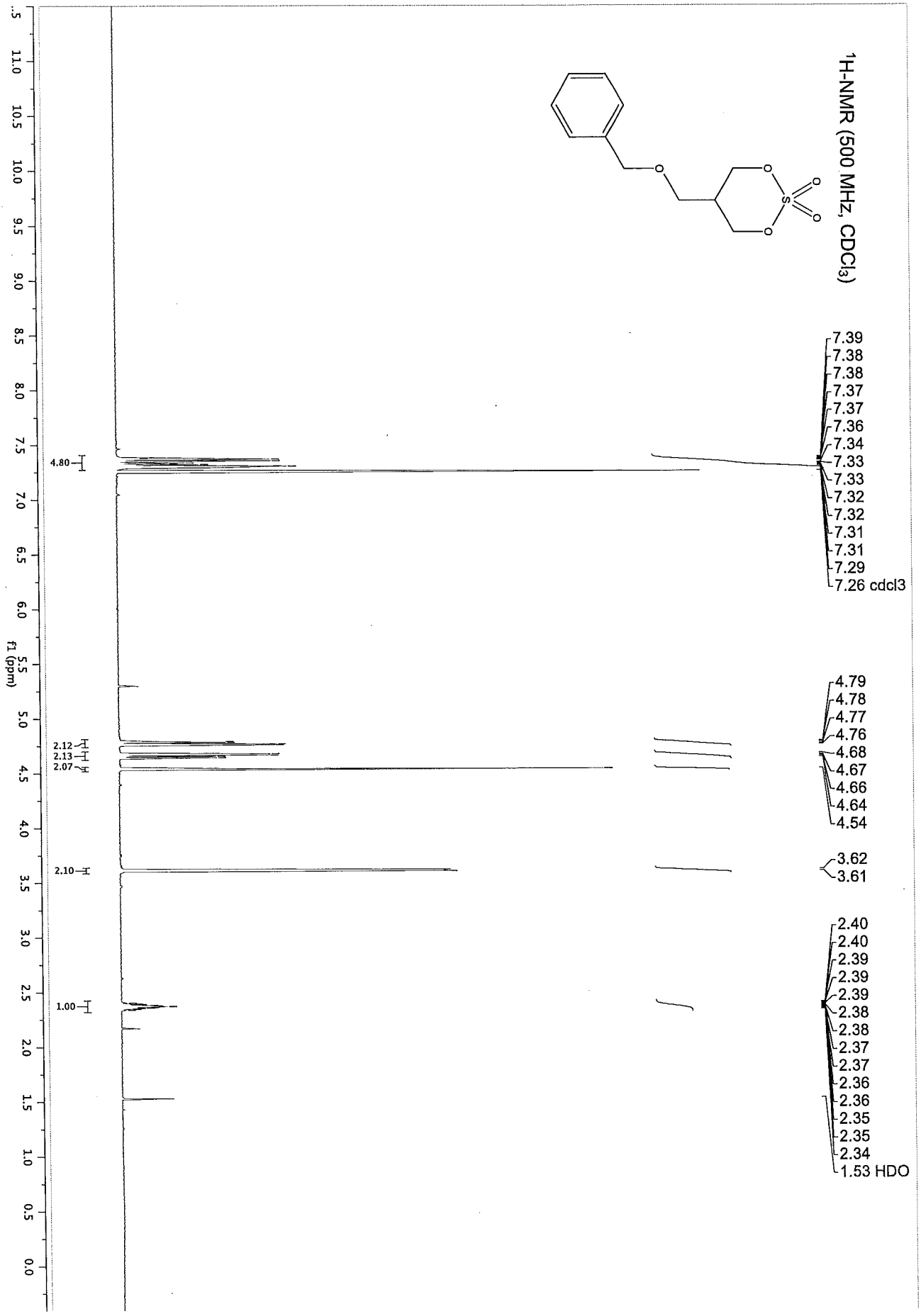

$^1$H-NMR (500 MHz, CDCl$_3$)
7.43
7.42
7.41
7.40
7.39
7.39
7.39
7.38
7.37
7.28
7.28
7.27 cdcl3
7.26
4.94
4.94
4.92
4.90
4.90
4.68
4.68
4.66
4.65
4.65
3.65
3.64
3.62
3.61
3.60
3.59
3.58
1.54 HDO
2.94
2.83
2.14
2.15
1.00
f1 (ppm)

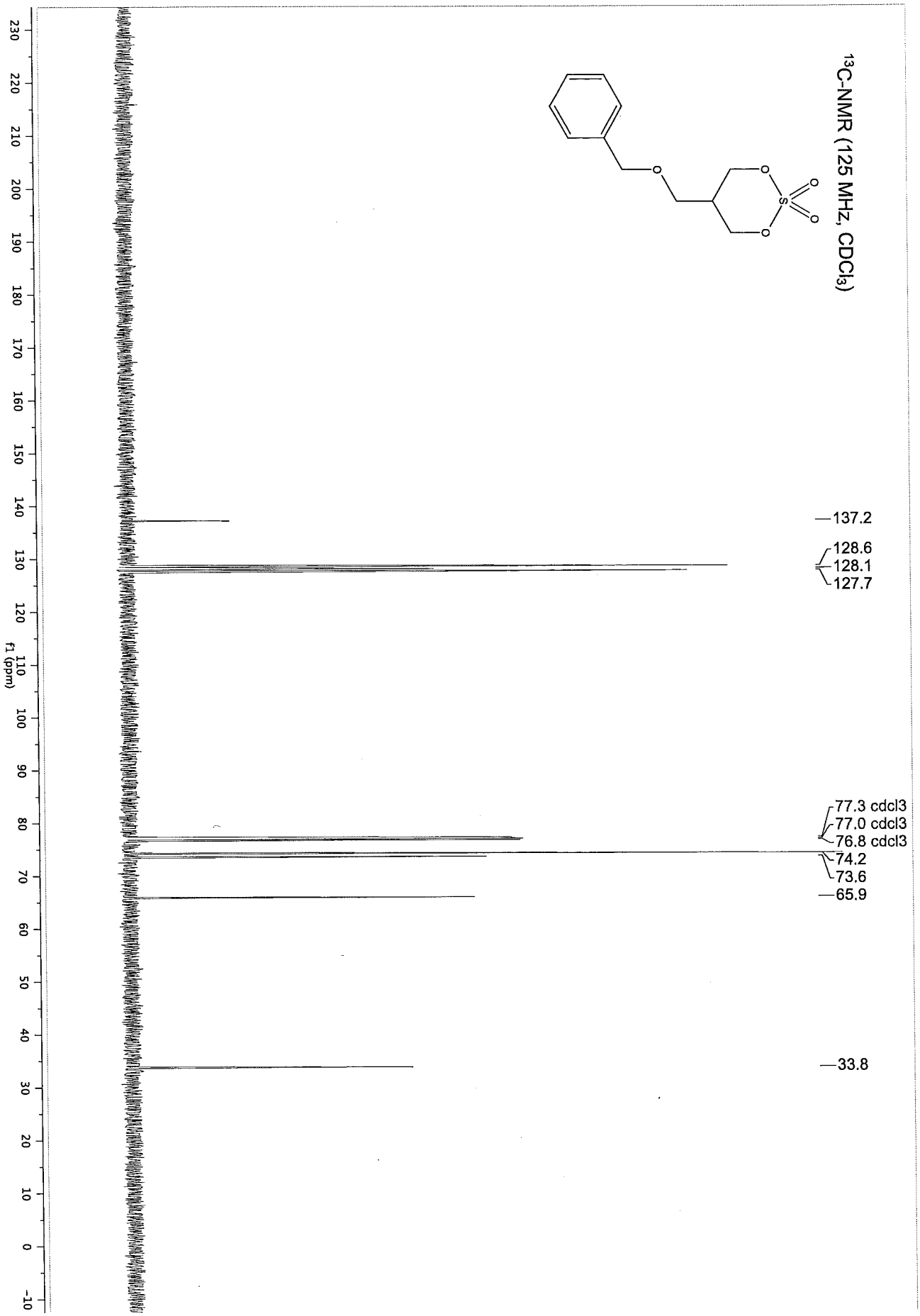
$^{13}$C-NMR (151 MHz, $CDCl_3$)

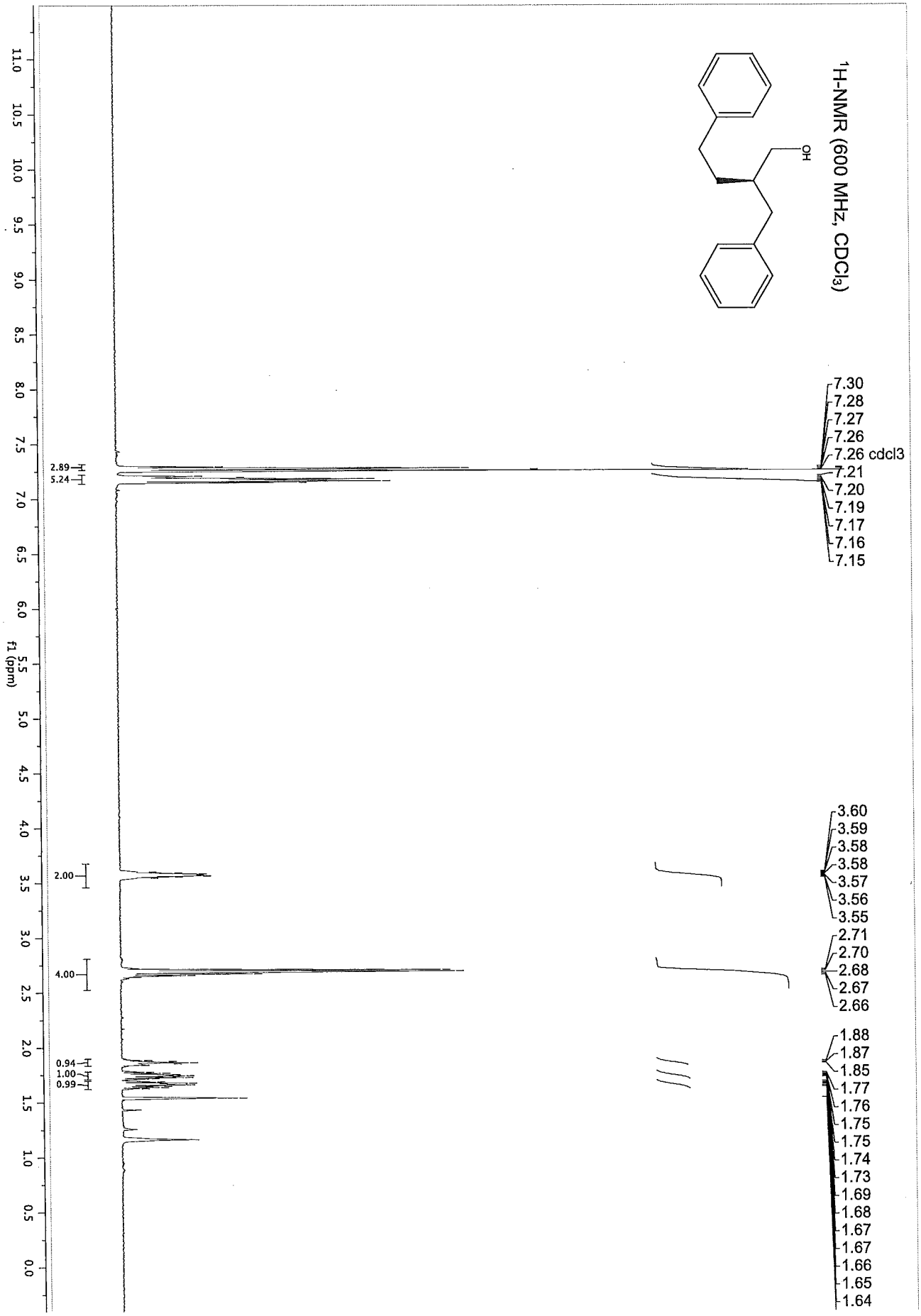


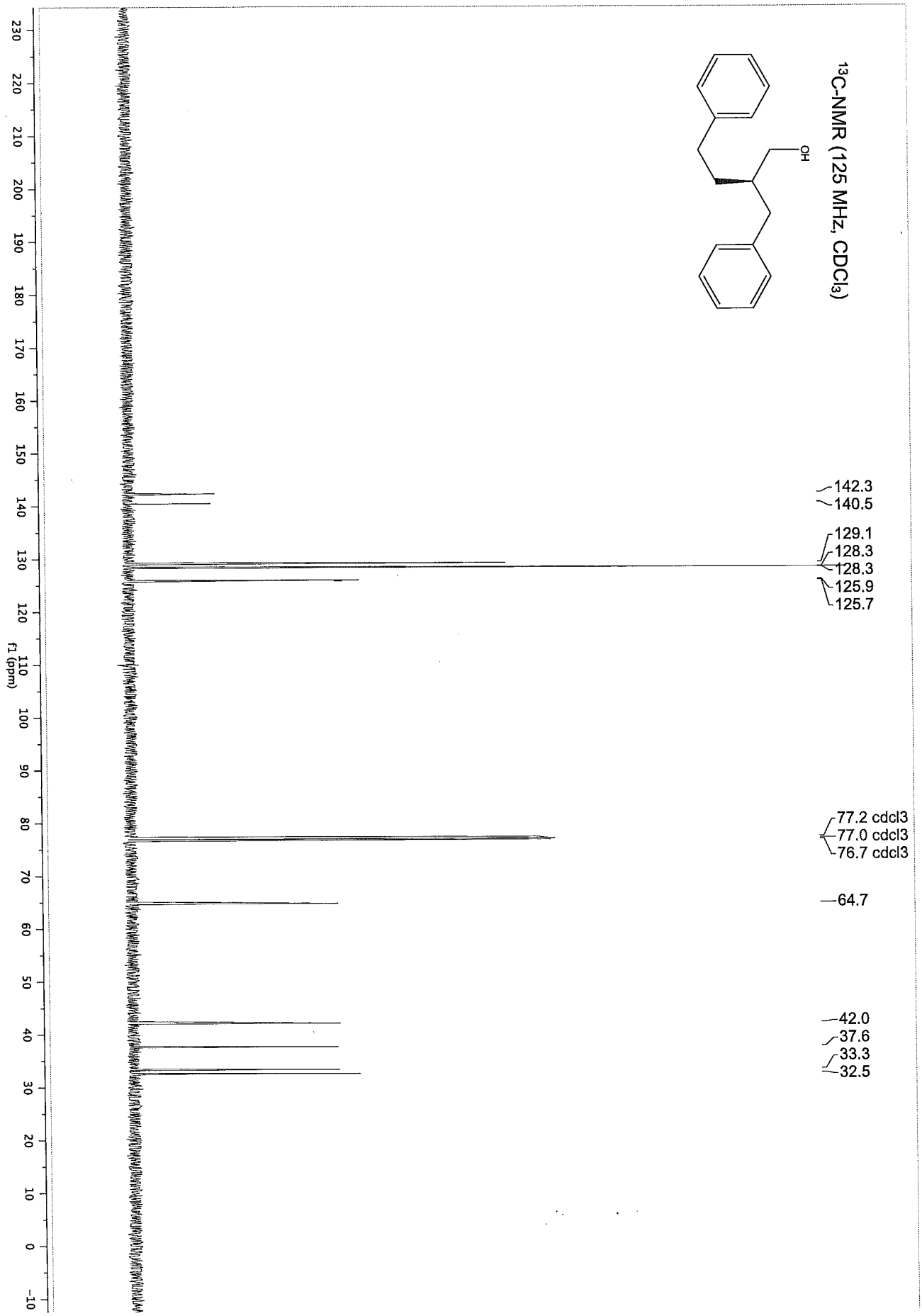

$^1$H-NMR (600 MHz, CDCl$_3$)
7.33
7.32
7.30
7.26 cdcl3
7.25
7.24
7.23
7.17
7.15
4.64
4.63
4.62
4.61
4.51
4.49
4.49
4.47
2.71
2.70
2.68
2.26
2.25
2.25
2.24
2.23
2.23
2.22
2.21
1.78
1.77
1.76
1.75
1.53 HDO
2.01
2.45
1.93
2.07
2.07
2.05
1.00
2.07
f1 (ppm)

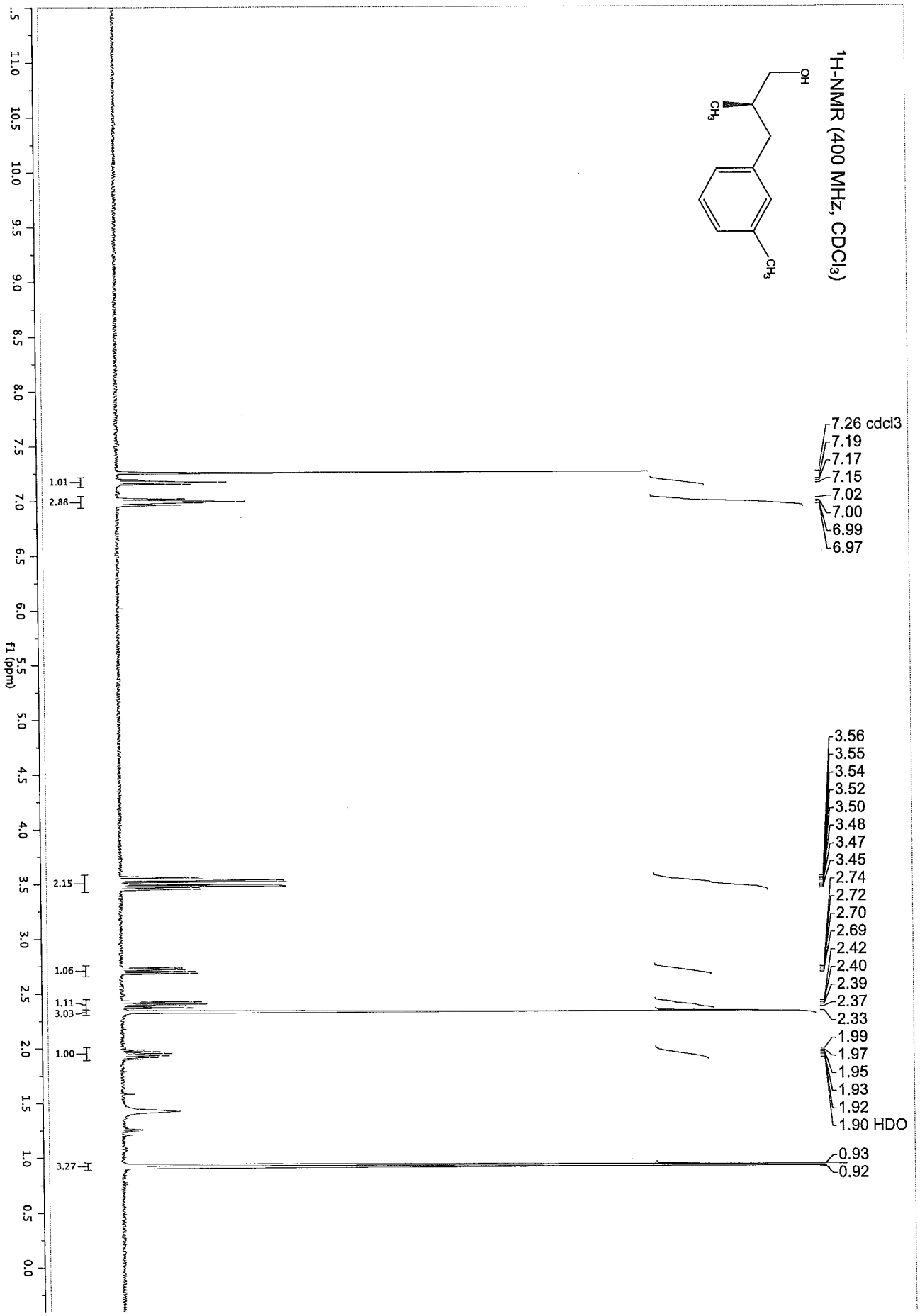

$^{13}$C-NMR (151 MHz, CDCl$_3$)
139.9
128.8
128.1
126.7
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
76.4
32.7
32.3
28.1
f1 (ppm)

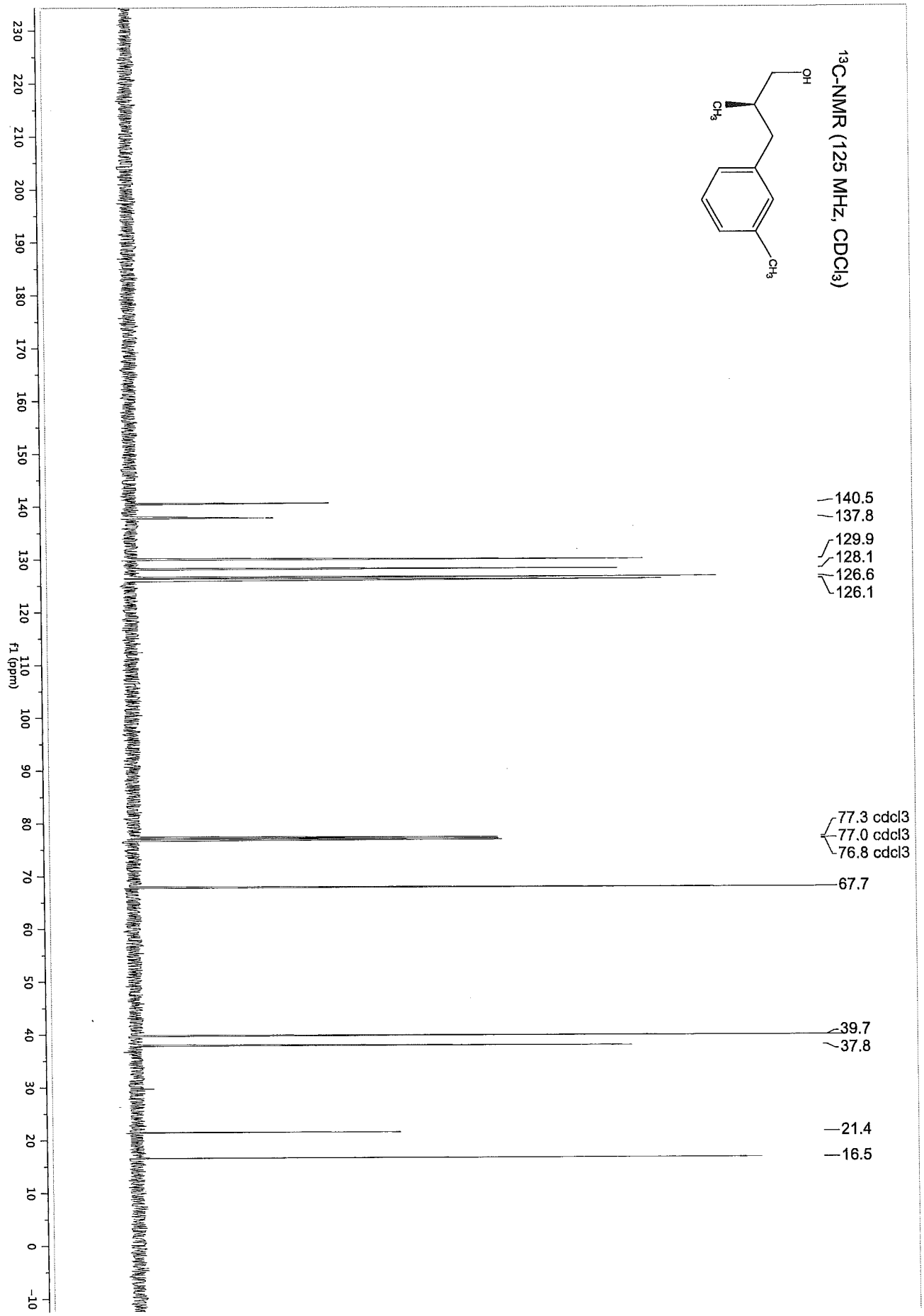

¹H-NMR (500 MHz, CDCl3)
7.39
7.38
7.38
7.37
7.37
7.36
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.29
7.26 cdcl3
4.79
4.78
4.77
4.76
4.68
4.67
4.66
4.64
4.54
3.62
3.61
2.40
2.40
2.39
2.39
2.39
2.38
2.38
2.37
2.37
2.36
2.36
2.35
2.35
2.34
1.53 HDO
4.80
2.12
2.13
2.07
2.10
1.00
f1 (ppm)

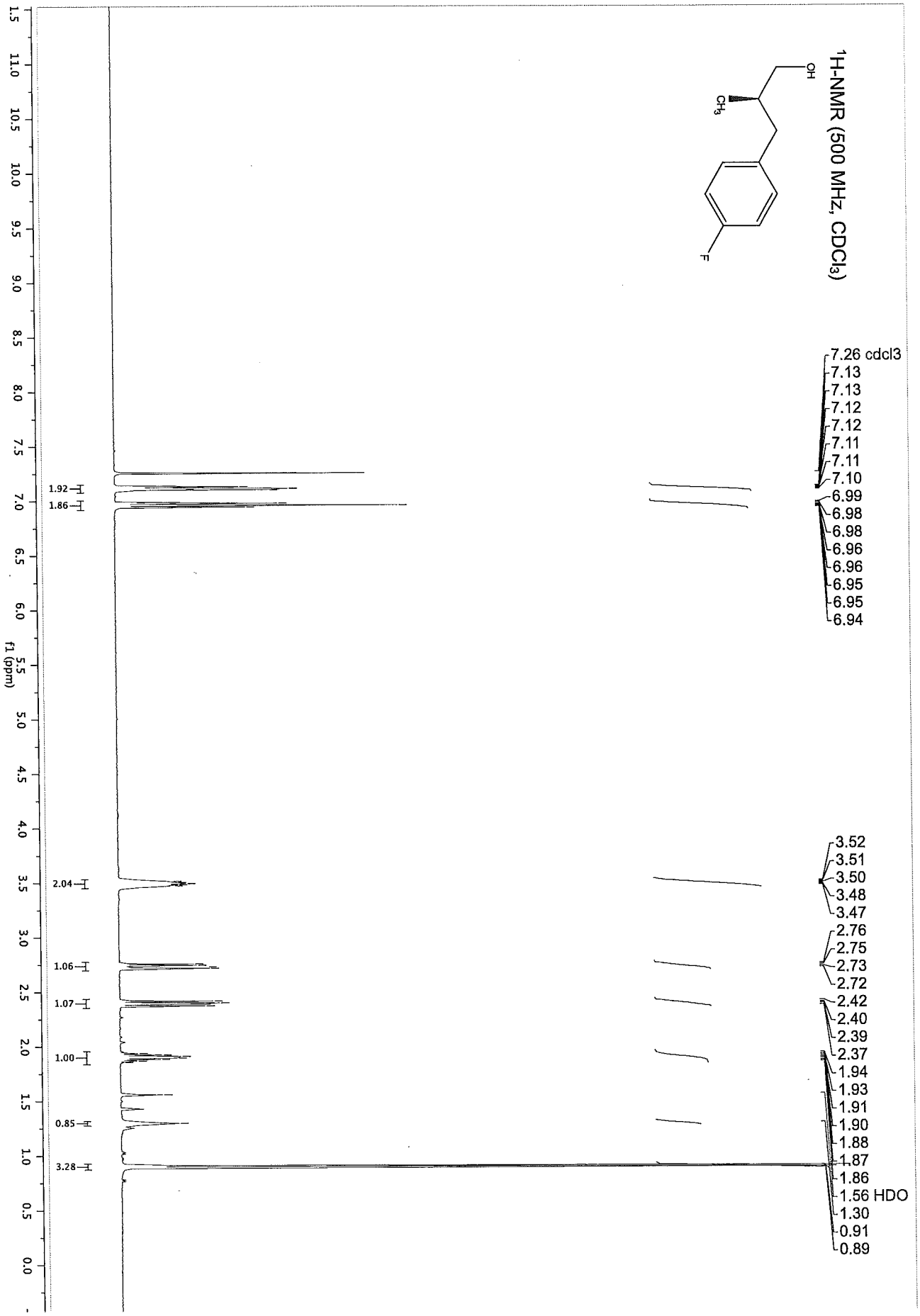

$^{13}$C-NMR (125 MHz, CDCl$_3$)
137.2
128.6
128.1
127.7
77.3 cdcl3
77.0 cdcl3
76.8 cdcl3
74.2
73.6
65.9
33.8
f1 (ppm)


$^1$H-NMR (600 MHz, CDCl$_3$)
OH
7.30
7.28
7.27
7.26
7.26 cdcl3
7.21
7.20
7.19
7.17
7.16
7.15
3.60
3.59
3.58
3.58
3.57
3.56
3.55
2.71
2.70
2.68
2.67
2.66
1.88
1.87
1.85
1.77
1.76
1.75
1.75
1.74
1.73
1.69
1.68
1.67
1.67
1.66
1.65
1.64
2.89
5.24
2.00
4.00
0.94
1.00
0.99
f1 (ppm)

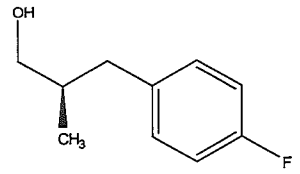

$^{13}$C-NMR (125 MHz, CDCl$_3$)
OH
142.3
140.5
129.1
128.3
128.3
125.9
125.7
77.2 cdcl3
77.0 cdcl3
76.7 cdcl3
64.7
42.0
37.6
33.3
32.5
f1 (ppm)

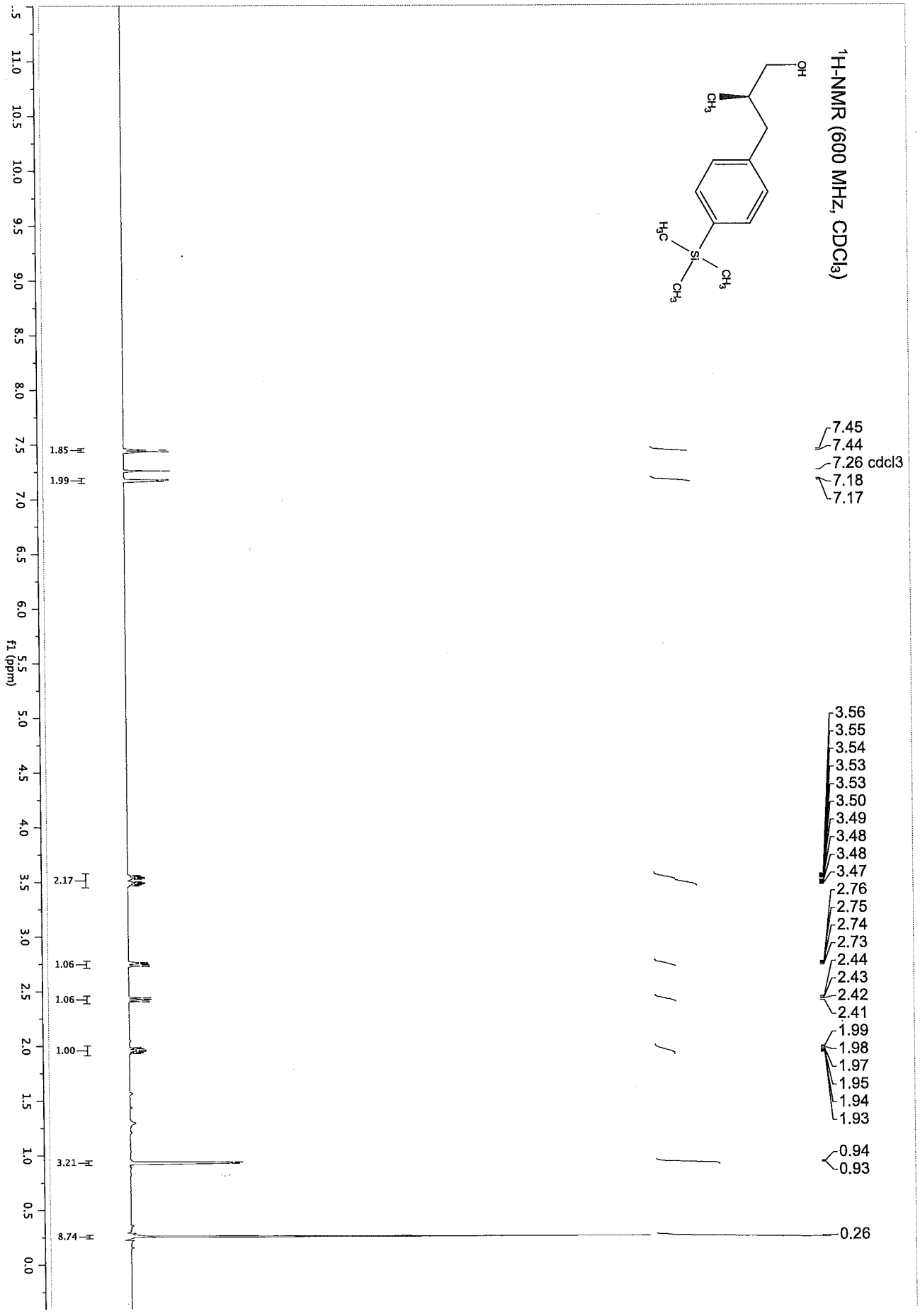

$^1$H-NMR (400 MHz, CDCl$_3$)
OH
CH$_3$
CH$_3$
7.26 cdcl3
7.19
7.17
7.15
7.02
7.00
6.99
6.97
3.56
3.55
3.54
3.52
3.50
3.48
3.47
3.45
2.74
2.72
2.70
2.69
2.42
2.40
2.39
2.37
2.33
1.99
1.97
1.95
1.93
1.92
1.90 HDO
0.93
0.92
1.01
2.88
2.15
1.06
1.11
3.03
1.00
3.27
f1 (ppm)

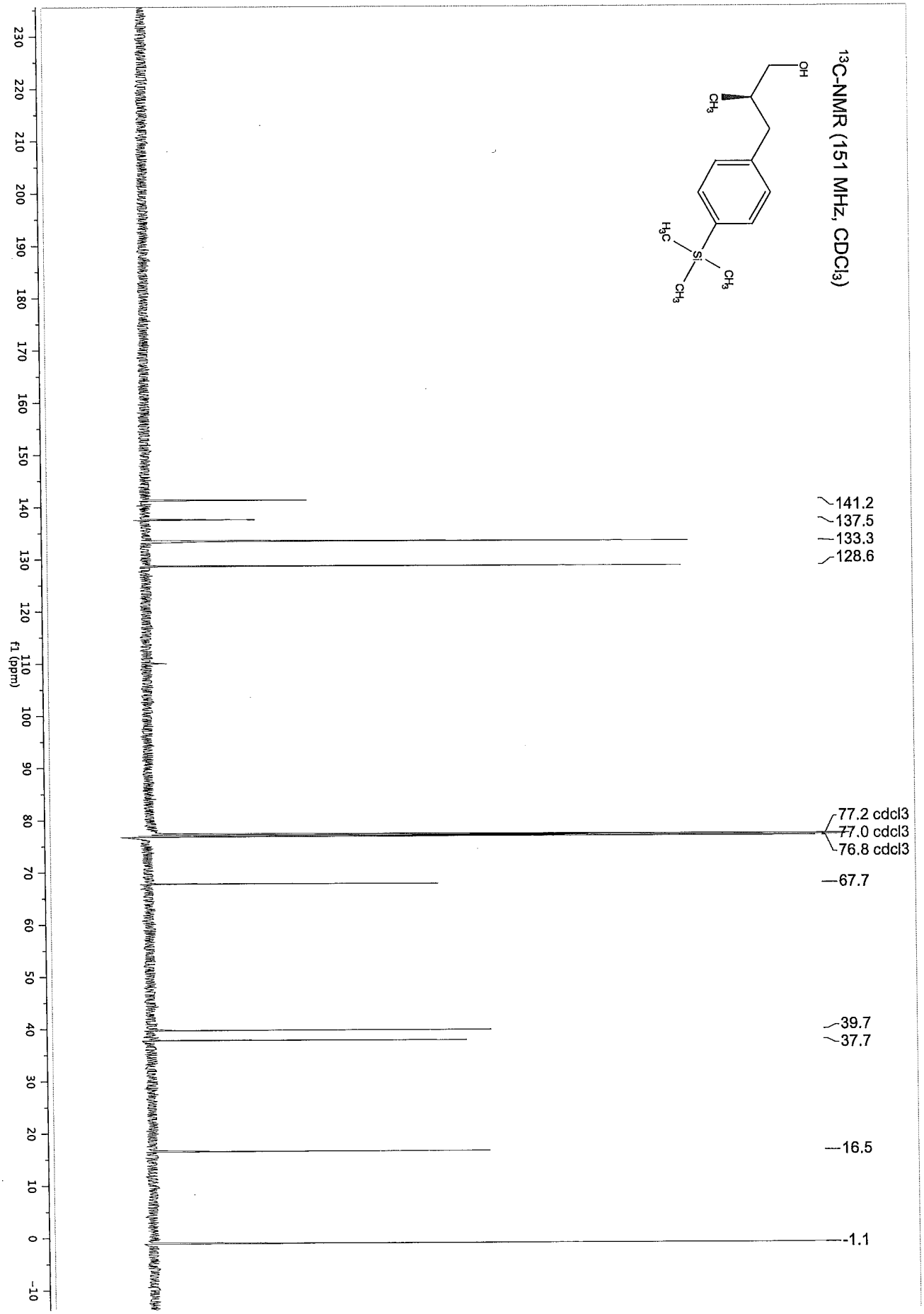

$^{13}$C-NMR (125 MHz, CDCl$_3$)
OH
CH$_3$
CH$_3$
140.5
137.8
129.9
128.1
126.6
126.1
77.3 cdcl3
77.0 cdcl3
76.8 cdcl3
67.7
39.7
37.8
21.4
16.5
f1 (ppm)

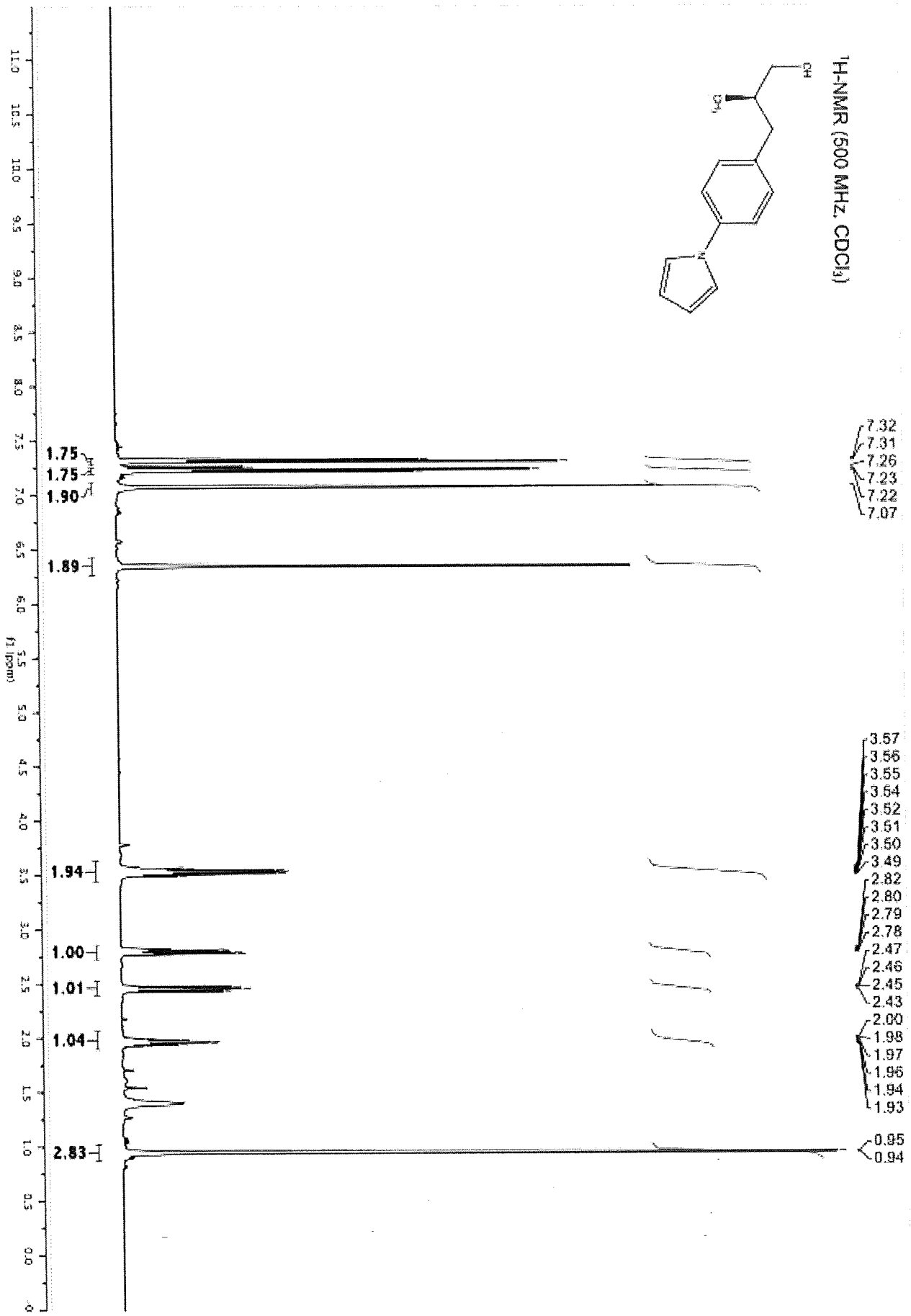

1H-NMR (500 MHz, CDCl3)
OH
CH3
F
7.26 cdcl3
7.13
7.13
7.12
7.12
7.11
7.11
7.10
6.99
6.98
6.98
6.96
6.96
6.95
6.95
6.94
3.52
3.51
3.50
3.48
3.47
2.76
2.75
2.73
2.72
2.42
2.40
2.39
2.37
1.94
1.93
1.91
1.90
1.88
1.87
1.86
1.56 HDO
1.30
0.91
0.89
1.92
1.86
2.04
1.06
1.07
1.00
0.85
3.28
f1 (ppm)

$^{13}$C-NMR (125 MHz, $CDCl_3$)

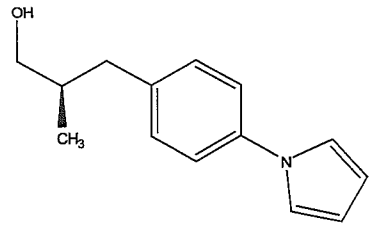


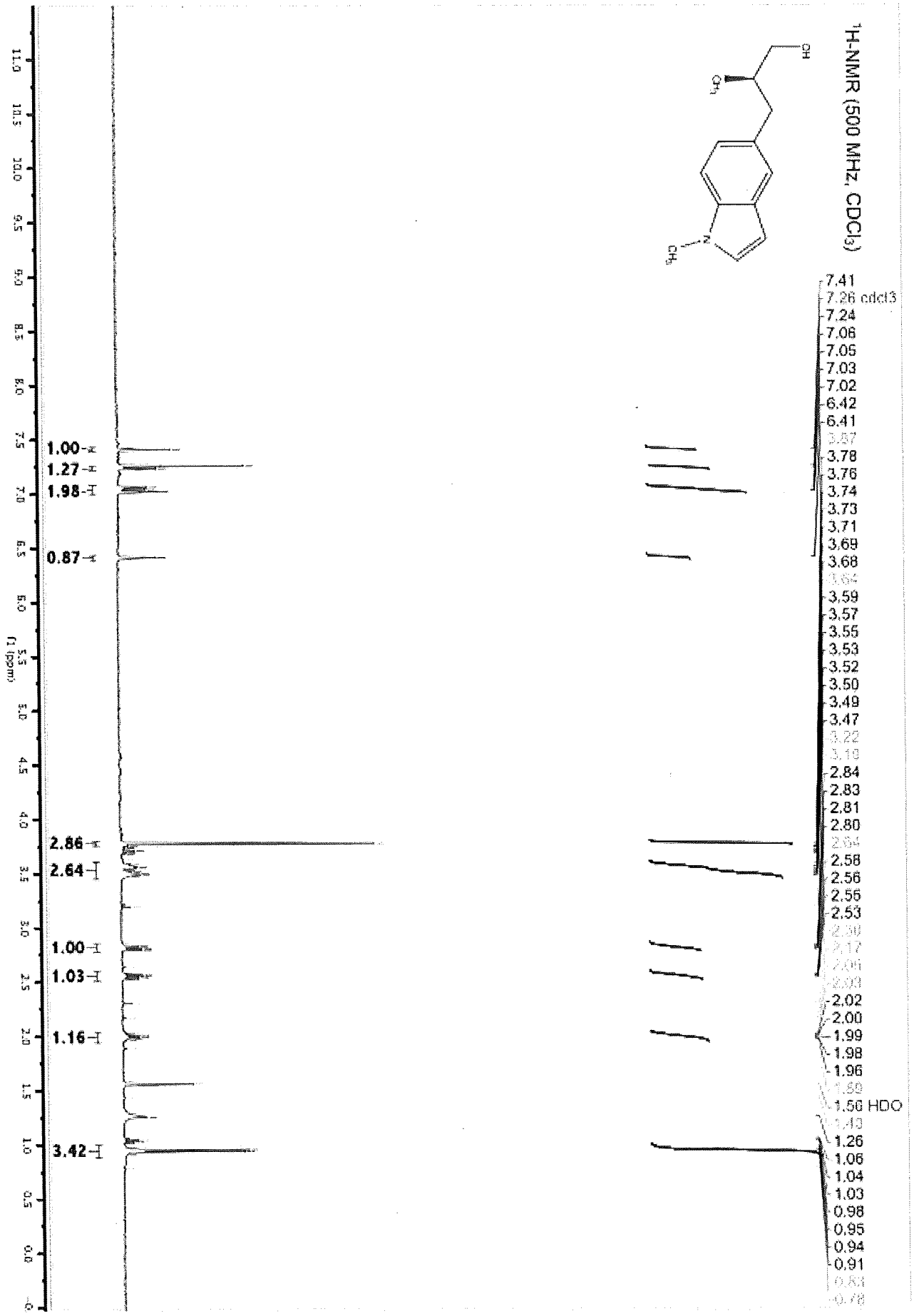

¹H-NMR (600 MHz, CDCl3)
OH
CH3
H3C
Si
CH3
CH3
7.45
7.44
7.26 cdcl3
7.18
7.17
3.56
3.55
3.54
3.53
3.53
3.50
3.49
3.48
3.48
3.47
2.76
2.75
2.74
2.73
2.44
2.43
2.42
2.41
1.99
1.98
1.97
1.95
1.94
1.93
0.94
0.93
0.26
1.85
1.99
2.17
1.06
1.06
1.00
3.21
8.74
f1 (ppm)

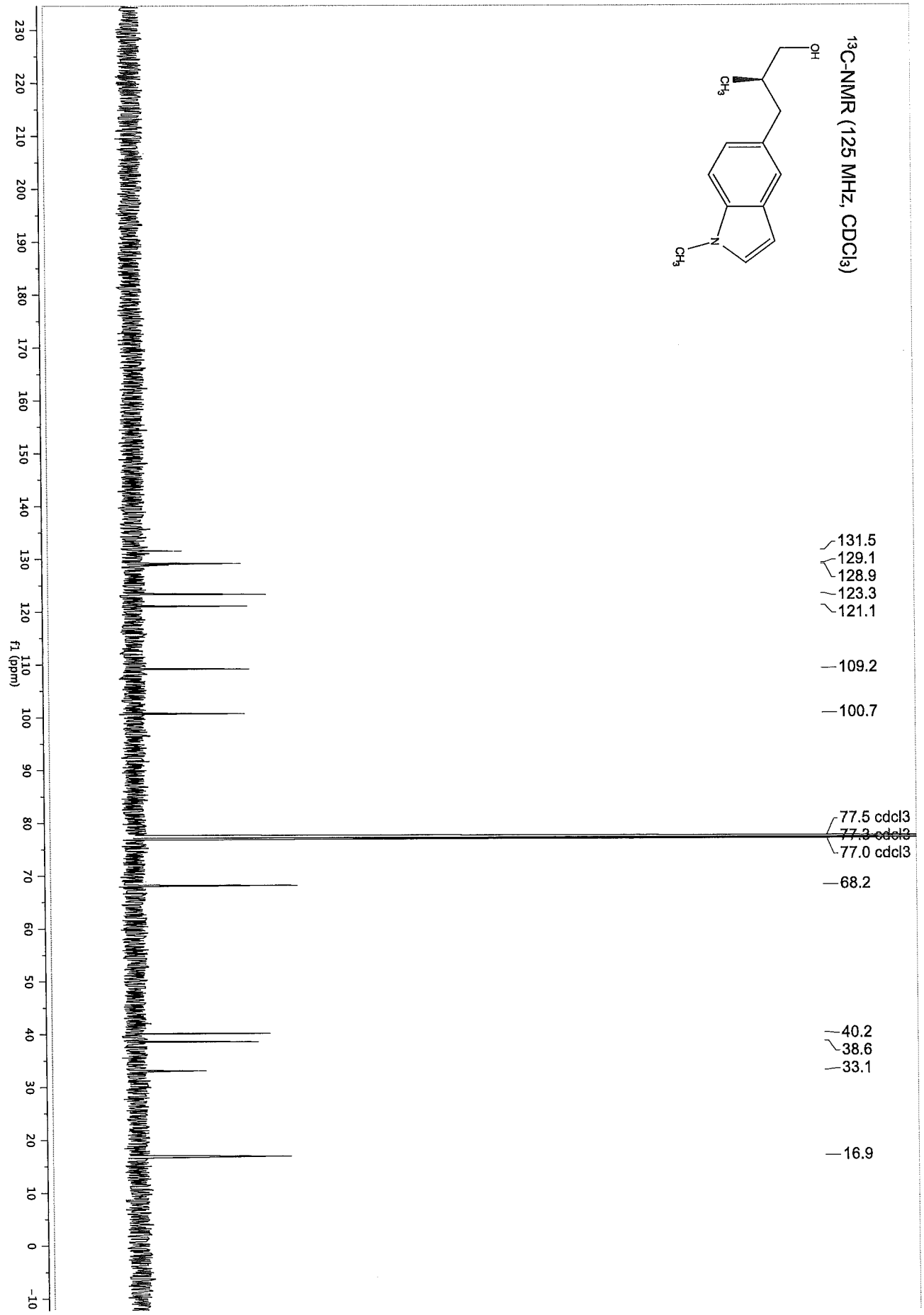

$^{13}$C-NMR (151 MHz, CDCl$_3$)
OH
CH$_3$
H$_3$C
Si
CH$_3$
CH$_3$
141.2
137.5
133.3
128.6
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
67.7
39.7
37.7
16.5
-1.1
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

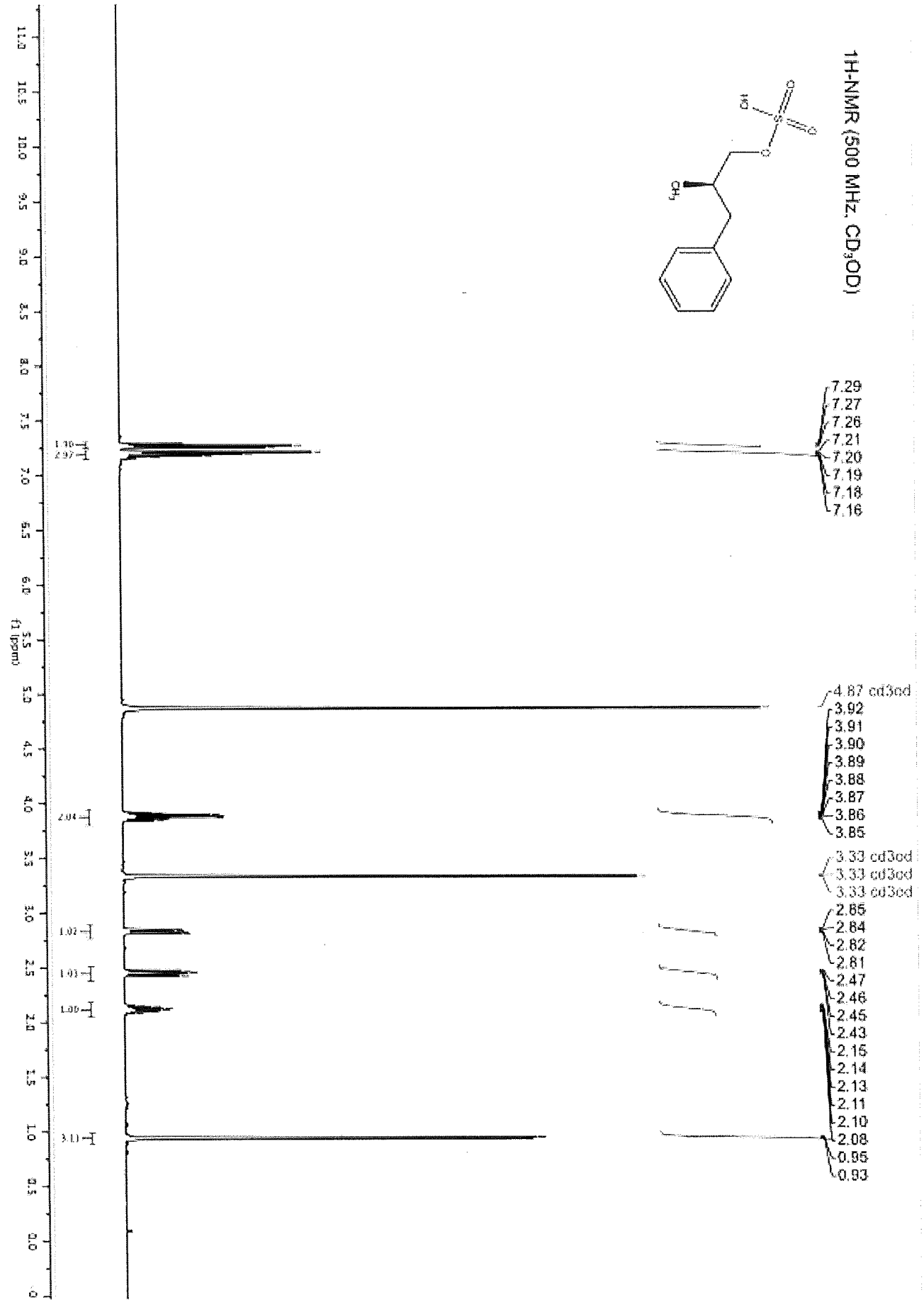

$^1$H-NMR (500 MHz, CDCl$_3$)
OH
1.75
1.75
1.90
1.89
1.94
1.00
1.01
1.04
2.83
7.32
7.31
7.26
7.23
7.22
7.07
3.57
3.56
3.55
3.54
3.52
3.51
3.50
3.49
2.82
2.80
2.79
2.78
2.47
2.46
2.45
2.43
2.00
1.98
1.97
1.96
1.94
1.93
0.95
0.94
f1 (ppm)

$^{13}$C-NMR (151 MHz, $CDCl_3$)




$^1$H-NMR (500 MHz, CDCl$_3$)
OH
CH$_3$
N
CH$_3$
f1 (ppm)
1.00
1.27
1.98
0.87
2.86
2.64
1.00
1.03
1.16
3.42
7.41
7.26 cdcl3
7.24
7.06
7.05
7.03
7.02
6.42
6.41
3.78
3.76
3.74
3.73
3.71
3.69
3.68
3.59
3.57
3.55
3.53
3.52
3.50
3.49
3.47
2.84
2.83
2.81
2.80
2.58
2.56
2.55
2.53
2.02
2.00
1.99
1.98
1.96
1.56 HDO
1.26
1.06
1.04
1.03
0.98
0.95
0.94
0.91


$^{13}$C-NMR (125 MHz, CDCl$_3$)
OH
CH$_3$
N
CH$_3$
131.5
129.1
128.9
123.3
121.1
109.2
100.7
77.5 cdcl3
77.3 cdcl3
77.0 cdcl3
68.2
40.2
38.6
33.1
16.9
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


1H-NMR (500 MHz, CD3OD)
7.29
7.27
7.26
7.21
7.20
7.19
7.18
7.16
4.87 cd3od
3.92
3.91
3.90
3.89
3.88
3.87
3.86
3.85
3.33 cd3od
3.33 cd3od
3.33 cd3od
2.85
2.84
2.82
2.81
2.47
2.46
2.45
2.43
2.15
2.14
2.13
2.11
2.10
2.08
0.95
0.93
f1 (ppm)

$^{13}$C-NMR (125 MHz, $CD_3OD$)



141.7
130.4
129.4
127.1
73.5
49.6 cd3od
49.5 cd3od
49.4 cd3od
49.2 cd3od
49.1 cd3od
48.9 cd3od
48.8 cd3od
40.6
36.7
16.9

f1 (ppm)

1H-NMR (600 MHz, CDCl3)
7.27 cdcl3
4.43
4.43
4.43
0.87
0.87
0.87
f1 (ppm)

$^{13}$C-NMR (151 MHz, CDCl3)

$^1$H-NMR (600 MHz, $CD_3OD$)



7.27
7.26
7.21
7.20
7.19
7.19
7.18
7.17

4.87 cd3od

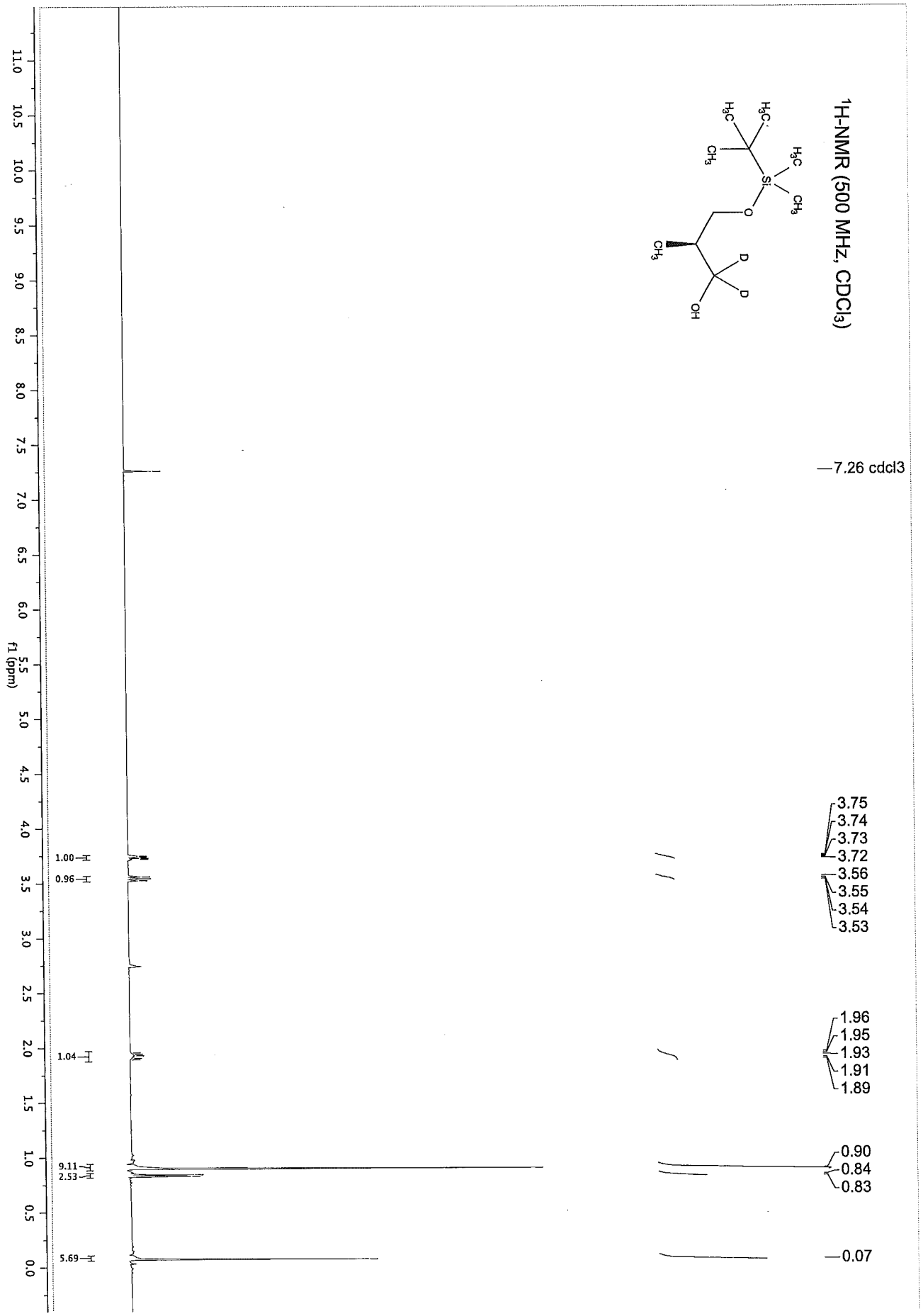
3.75

3.33 cd3od

2.75

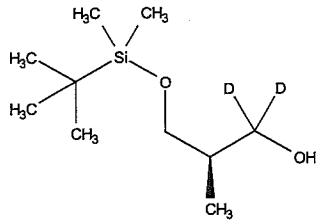
0.55

$^{13}$C-NMR (151MHz, $CD_3OD$)

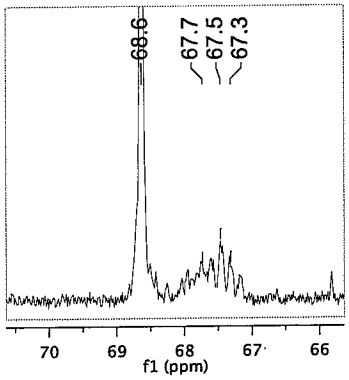

$^1$H-NMR (500 MHz, CDCl$_3$)
—7.26 cdcl3
3.75
3.74
3.73
3.72
3.56
3.55
3.54
3.53
1.96
1.95
1.93
1.91
1.89
0.90
0.84
0.83
—0.07
1.00
0.96
1.04
9.11
2.53
5.69
f1 (ppm)

403

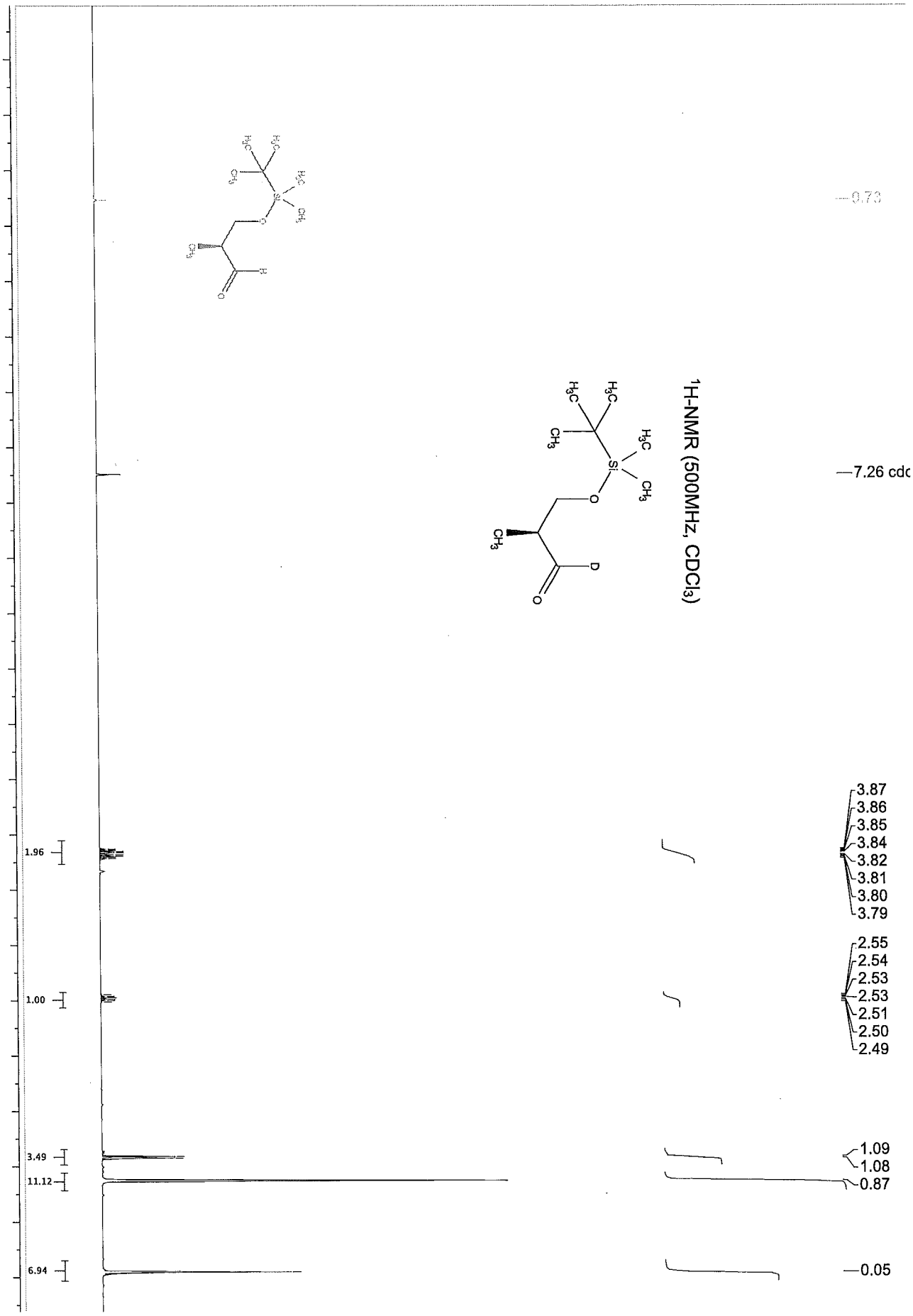
$^{13}$C-NMR (151 MHz, $CDCl_3$)



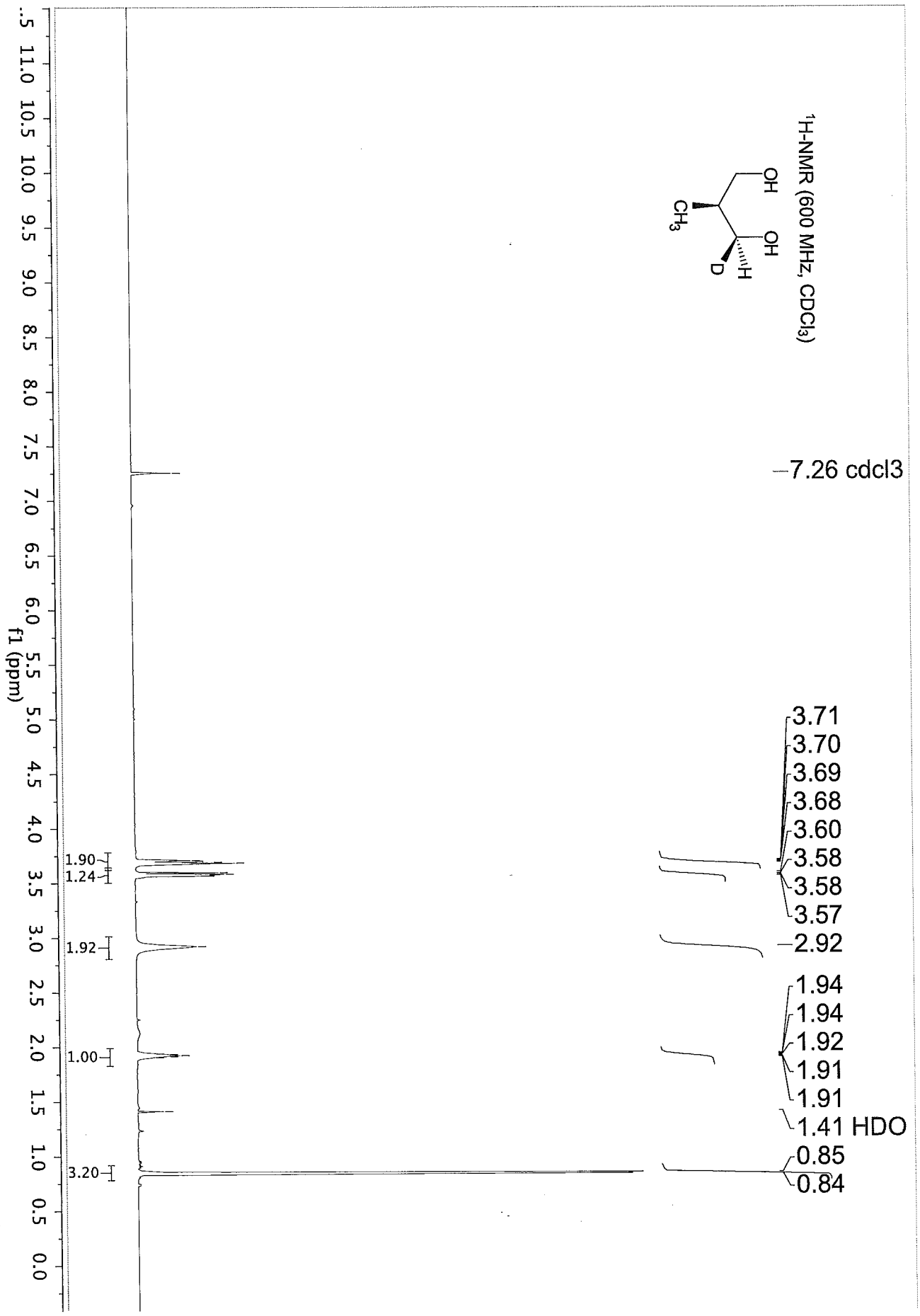

77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
68.6
67.5
36.9
36.9
25.8
18.2
13.0
-5.6




230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


$^1$H-NMR (500MHz, CDCl$_3$)
—0.73
—7.26 cdc
3.87
3.86
3.85
3.84
3.82
3.81
3.80
3.79
2.55
2.54
2.53
2.53
2.51
2.50
2.49
1.09
1.08
0.87
—0.05
1.96
1.00
3.49
11.12
6.94

$^{13}$C-NMR (151MHz, CDCl$_3$)
204.7
204.5
204.4
204.2
77.2
77.0
76.8
63.4
48.6
25.8
18.2
10.2
-5.5
f1 (ppm)
205.0
204.0
203.0


$^1$H-NMR (600 MHz, CDCl$_3$)
OH
OH
CH$_3$
H
D
7.26 cdcl3
3.71
3.70
3.69
3.68
3.60
3.58
3.58
3.57
2.92
1.94
1.94
1.92
1.91
1.91
1.41 HDO
0.85
0.84
1.90
1.24
1.92
1.00
3.20
f1 (ppm)

$^{13}$C-NMR (151 MHz, CDCl$_3$)
OH
OH
CH$_3$
D
H
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
67.7
67.4
67.3
67.1
37.0
13.0
67.4
67.3
67.1
67.4
67.2
67.0
f1 (ppm)
f1 (ppm)

$^1$H-NMR (500 MHz, $CDCl_3$)

$^{13}$C-NMR (125 MHz, $CDCl_3$)

$^1$H-NMR (600 MHz, $CDCl_3$)

$^{13}$C-NMR (151 MHz, $CDCl_3$)




140.5
129.1
128.2
125.8
77.2 cdcl3
77.0 cdcl3
76.8 cdcl3
67.6
39.4
39.3
39.2
37.7
16.4

# Chapter 4

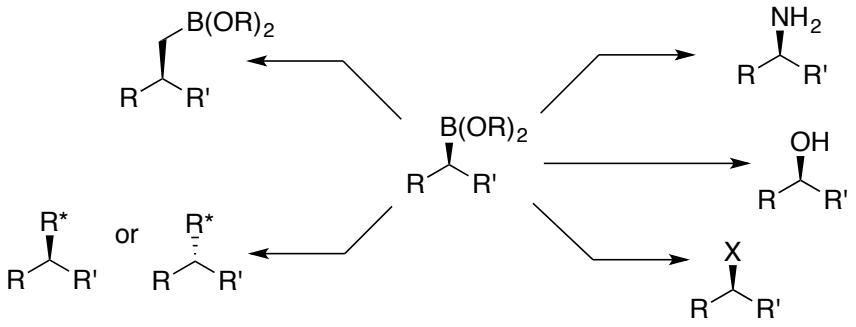
# One Pot, Asymmetric Diboration Allylation Cross-Coupling Method to Access Elaborate Carbocyclic Frameworks

## 4.1 Introduction

Organoboronate esters are important intermediates that can be used in a diverse range of transformations, making them a powerful tool in synthesis.[1] A majority of organoboron compounds are easy to handle, stable and synthesized from cheap, readily available materials. Simple organoboronate esters can undergo oxidation[2], amination[3], halogenation[4], homologation[5] and a variety of cross-coupling reactions that proceed with high levels of stereospecificity (Scheme 4.1).

[1] Xu, L.; Zhang, S.; Li, P. *Chem. Soc. Rev.* **2015**, *44*, 8848.
[2] Zweifel, G.; Brown, H. C. *Org. React.* **1963**, *13*, 1. (b) Brown, H. C.; Snyder, C.; Subba Rao, B. C.; Zweifel, G. *Tetrahedron* **1986**, *42*, 5505. (c) Kabalka, G. W.; Wadgaonkar, P. P.; Shoup, T. M. *Organometallics* **1990**, *9*, 1316.
[3] (a) Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Am. Chem. Soc.* **1973**, *95*, 2394. (b) Brown, H. C.; Kim, K. W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc.* **1986**, *108*, 6761. (c) Knight, F. I.; Brown, J. M.; Lazzari, D.; Ricci, A.; Blacker, A. J. *Tetrahedron* **1997**, *53*, 11411. (d) Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem. Eur. J.* **2000**, *6*, 1840. (e) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449. (f) Zhu, C.; Li, G.; Ess, D. H.; Falk, J. R.; Kürti, L. *J. Am. Chem. Soc.* **2012,** *134*, 18253**.**
[4] Sanford, C.; Rasappan, R.; Aggarwal, V. K. *J. Am. Chem. Soc.*, **2015**, 137, 10100.
[5] Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc.* **1983**, *105*, 2077.

**Scheme 4.1: Stereospecific Reactions of Simple Organoboronates**




Additionally, if the organoboron is adjacent to an alkene, these allylborons can participate in allylation and crotylation reactions of carbonyl compounds as well as a variety of different cross-coupling reactions. Additions of allylboron reagents to carbonyls is known to proceed in a closed, chair-like transition state, which allows for predictable diastereoselective allylation reactions.[6] During the past decade, the Morken lab has made several contributions to the field of asymmetric diboration of unsaturated systems,[7] as well as expanding the tool box of reactions available to further transform the resulting boronate esters.[8] In this chapter, I will present the development of a one pot-diboration,

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[6] For reviews on allylation reactions see: (a) Srebnik, M.; Ramachandran, P. V. *Aldrichimica Acta* **1987**, *20*, 9. (b) Roush, W. R. *In Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 2*, pp. 1-53

[7] a) Morgan, J. B.; Morken, J. P. *Org. Lett.*, **2003**, *5*, 2573. (b) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.*, **2003**, *125*, 8702. (c) Miller, S. P.; Morgan, J. B.; Nepveux, F. J.; Morken, J. P. *Org. Lett.*, **2004**, *6*, 131. (d) Morgan, J. P.; Morken, J. P. *J. Am. Chem. Soc.*, **2004**, *126*, 15338. (e) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.*, **2004**, *126*, 16328. (f) Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem.*, **2005**, *70*, 9538. (g) Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.*, **2013**, *135*, 11222. (h) Fang, L.; Yan, L.; Haeffner, F.; Morken, J. P. *J. Am. Chem. Soc.*, **2016**, *138*, 2508.

[8] (a)Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.*, **2005**, *7*, 5505. (b) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.*, **2006**, *128*, 74. (c) Pelz, N. F.; Morken, J.

allylation, cross-coupling method to access elaborate, enantioenriched carbocyclic structures. The utility of this method will be highlighted in efforts to synthesize xaimycin A and bromophycolide F.

## 4.2 Background Allylic Boronate Synthesis and Utility

### *4.2.1 Synthesis of Allyic Boronates*

Due to the utility of allylic boronates in carbon-carbon bond forming reactions; efficient, regio- and enantioselective methods to synthesize these motifs is of particular interest to the synthetic community. Historically, allylic boronates have been synthesized *via* stoichiometric allylmetal additions to boron-containing electrophiles,[9] or through homologation of vinylboronates.[10] These methods have several drawbacks: they the use stoichiometric metal species, they require strongly basic conditions, and they are not compatible in the synthesis of allylic boronates with diverse functional groups. To address

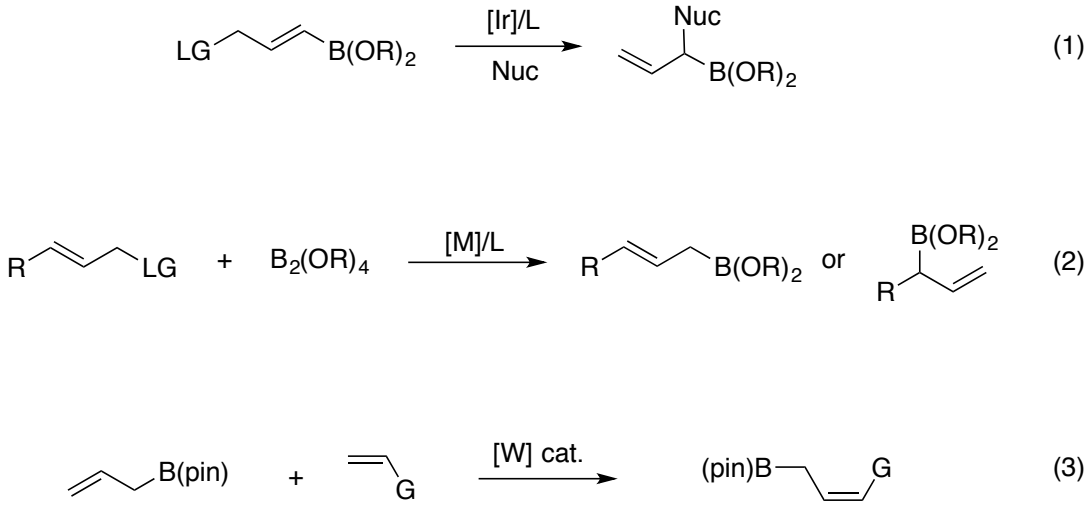
P. *Org. Lett.*, **2006**, *8*, 4557. Cho, H. Y.; Morken, J. P. *J. Am. Chem. Soc.*, **2008**, *130*, 16140. (d) Cho, H. Y.; Yu, Z.; Morken, J. P. *Org. Lett.*, **2011**, *13*, 5267. (e) Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. *Nature.* **2014**, *505*, 386. (f) Blaisdell, T. P.; Morken, J. P. *J. Am. Chem. Soc.*, **2015**, *137*, 8712.

[9] For representative examples with various metals; (a) Brown, H. C.; Rangaishenvi, M. V. *Tetrahedron Lett.* **1990**, *31*, 7113 (b) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (c) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem*. **1990**, *55*, 1868 (d) Hoffmann, R. W.; Zeiss, H. *J. Org. Chem*. **1981**, *46*, 1309. (e) Hoffman, R.W.; Feussner, G.; Zeiss, H.; Schultz, S. *J. Organomet. Chem*. **1980**, *187*, 321.

[10] (a) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc*. **1980**, *102*, 7588. (b) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (c) Brown, H. B.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem.* **1986**, *51*, 3150. (d) Althaus, M.; Mahmmod, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 4025.

these limitation, metal-catalyzed allylic substitution (Scheme 4.2, eq. 1)[11] and alkylation (Scheme 4.2, eq. 2)[12] methods have become popular in the synthesis of allylic boronates, since several of these strategies can be used to access enantioenriched allylic boronates. More recently, Hoveyda and co-workers have developed a tungsten-based olefin metathesis catalyst, which can be used for the Z-selective cross-metathesis with allylboronate esters (Scheme 4.2, eq. 3).[13]

**Scheme 4.2: Classical Methods for Synthesis of Allylboronates**




[11] For representative examples: (a) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem Soc*. **2005**, *127*, 16034. (b) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14826. (c) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634. (d) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, T. D. *J. Am. Chem. Soc.* **2011**, *133*, 2410. (e) Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett*. **2012**, *14*, 1416.

[12] For representative examples: (a) Peng, F.; Hall, D. G.; *Tetrahedron Lett.* **2007**, *48*, 3305. (b) Carosi, L.; Hall, D. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 5913.

[13] Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026.

Though the above metal-catalyzed substitution methods are very useful, another strategy to access allylboronates is the difunctionalization of unsaturated systems through hydroboration[14] or diboration.[15] In 1989, Suzuki and co-workers demonstrated the Pd-catalyzed hydroboration of 1,3-butadienes with catecholborane (Scheme 4.3, eq. 1).[16] This is an efficient strategy for the hydroboration of 2-substituted or 2,3-disubstituted butadienes, but the method fails for terminally substituted dienes. In 2010, Morken was able to expand the scope of diene hydroboration to include terminally substituted dienes (Scheme 4.3, eq. 2). They discovered that a nickel catalyst was critical for the reaction, whereas Pd and Pt catalysts failed.[17]

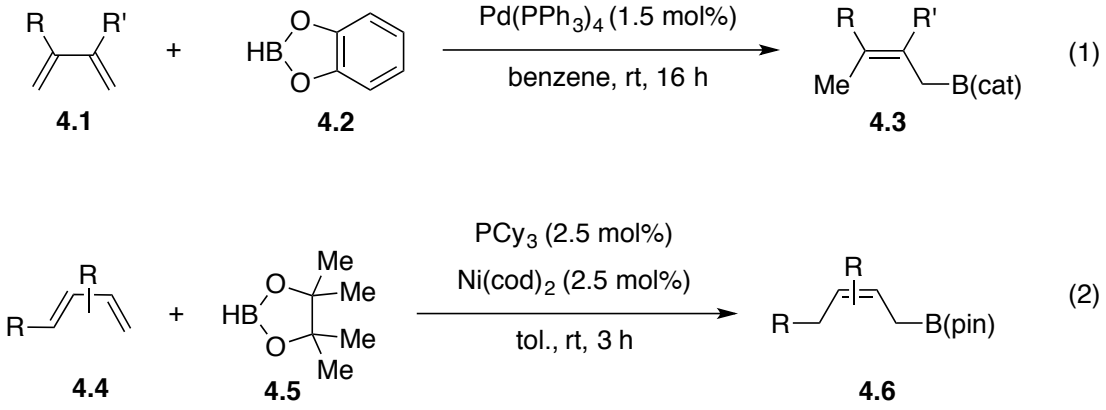
[14] Representative examples see: (a) Matsumoto, Y.; Naito, M.; Hayashi, T. *Organometallics* **1992**, *11*, 2732. (b) Yamamoto, Y.; Fujikawa, R.; Yamada, A.; Miyaura, N. *Chem. Lett*. **1999**, 1069. (c) Wu, J. Y.; Moreau, B.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 12915

[15] Representitive examples see: (a) Morgan, J. B.; Morken, J. P. *Org. Lett.* **2003**, *5*, 2573. (b) Ballard, E.; Morken, J. P.; *Synthesis*, **2004**, *9*, 1321. (c) Pelz, A. R.; Woodward, A. R.; Burks, H. E.; Seiber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328. Cho, H. Y.; Morken, J. P. *J. Am*. *Chem. Soc.* **2008**, *30*, 16140. Ely, R. J.; Morken, J. P. *Org. Lett.* **2010**, *12*, 4348.

[16] Satoh M, Nomoto Y, Miyaura N, Suzuki A. *Tetrahedron Lett.* **1989**, *30*, 3789.

[17] Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 2534.

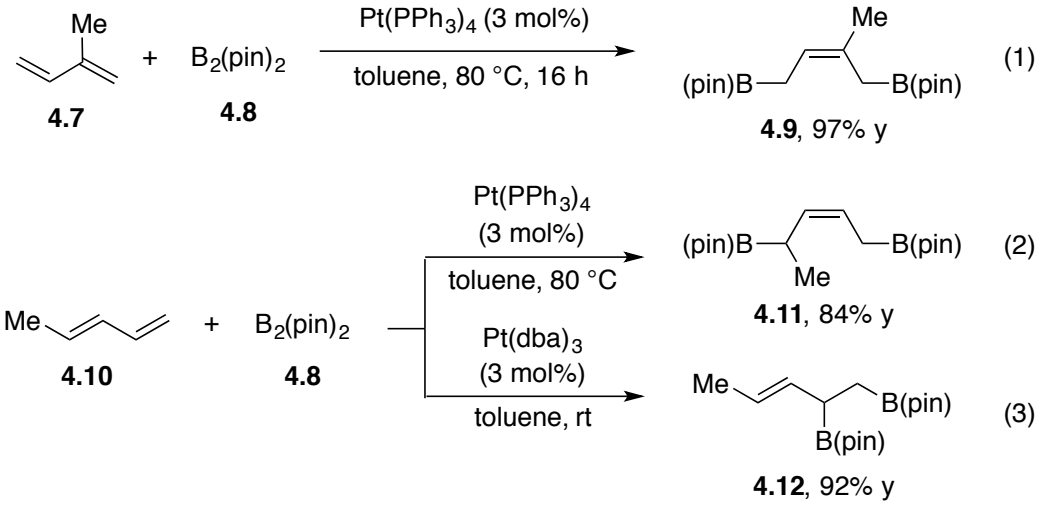
**Scheme 4.3: 1,4-Hydroboration of Dienes to Access Allylboronates**




Hydroboration is a useful system to access allylboronates, but diboration of similar unsaturated systems offers an added benefit of an additional functional handle in the product. Miyaura and co-workers presented the first metal catalyzed diboration of 1,3-dienes in 1996.[18] Diboration of isoprene with catalytic Pt(0) at 80 °C in toluene resulted in exclusive formation of the 1,4-addition product **4.9** in 93% yield (Scheme 4.4, eq. 1). The next year, Miyaura demonstrated that simply changing the catalyst from $Pt(PPh_3)_4$ to a non-phosphine ligated platinium, $Pt(dba)_2$, resulted in a complete reversal in regioselectivity to favor 1,2-diboration (Scheme 4.4, eq. 2,3).[19] The authors note that further studies are in progress to elucidate the mechanism. However, the 1,4-addition product is consistent with formation of a $\pi$-allylPt(II) intermediate during the reaction.[23]

[18] Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Comm.* **1996**, 2073.
[19] Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Comm.* **1997**, 689.

**Scheme 4.4: Miyaura Diboration of 1,3-Dienes to Access Allylboronates**



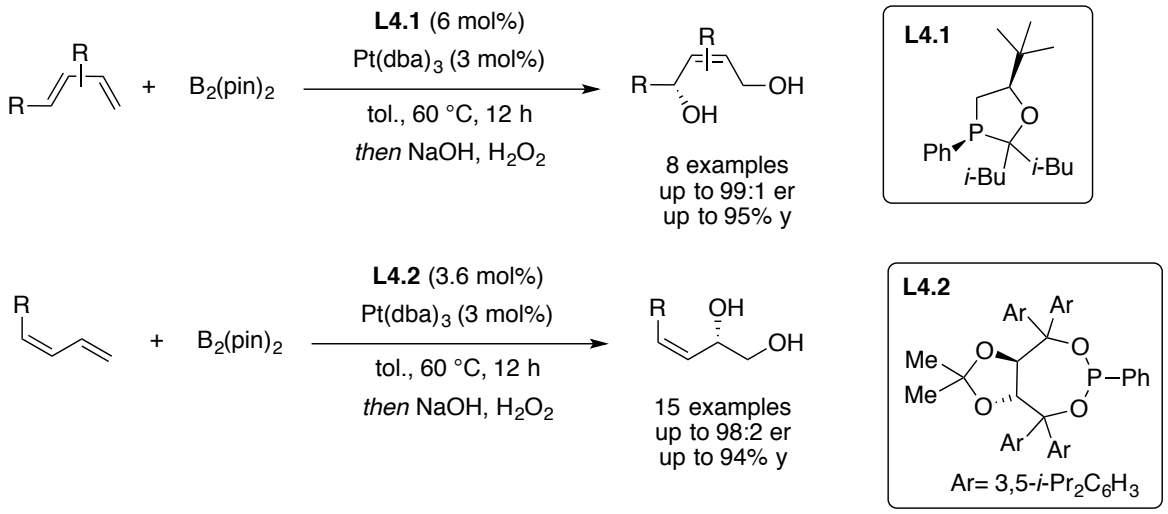

The above reactions indicate that the choice of ligand on platinum could be used to influence the regioselectivity of the reaction. Thus one would expect that with the correct choice of chiral ligand both enantioselectivity and regioselectivity of the process could be controlled.[20] The products could then be used in stereospecific allylation reactions with carbonyl compounds. Over a decade after the development of the Miyaura diboration, Morken and co-workers presented the platinum-catalyzed enantioselective 1,4-diboration of 1,3-dienes under the influence of a new chiral ligand, Oxaphos **L4.1** (Scheme 4.5, eq. 1).[21] A year later, the same group was able to develop a complimentary

[20] For diastereoselective diboration of dienes with chiral diboron species see: (a) Clegg, W.; Johann, T. R. F.; Marder, T. B.; Normal, N. C.; Orpen, A. G.; Peakman, T. M.; Quayle, M. J.; Rice, C. R.; Scott, A. J. *J. Chem. Soc., Dalton Trans.* **1998**, 1431. (b) Morgan, J. B.; Morken, J. P. *Org. Lett.* **2003**, *5*, 2573. For initial discoveries in asymmetric diene diboration see: (a) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *31*, 9134. (b) Hong, K.; Morken, J. P. *J. Org. Chem*. **2011**, *76*, 9102.

[21] Schuster, C. H.; Morken, J. P. *Ang. Chem. Int. Ed.* **2011**, *50*, 7906.

asymmetric 1,2-diboration of cis-1,3-dienes (Scheme 4.5, eq. 2), this time employing a TADDOL-derived phosphonite ligand **L4.2**.[22]

**Scheme 4.5: Asymmetric Diboration of Dienes to Access Allylboronates**

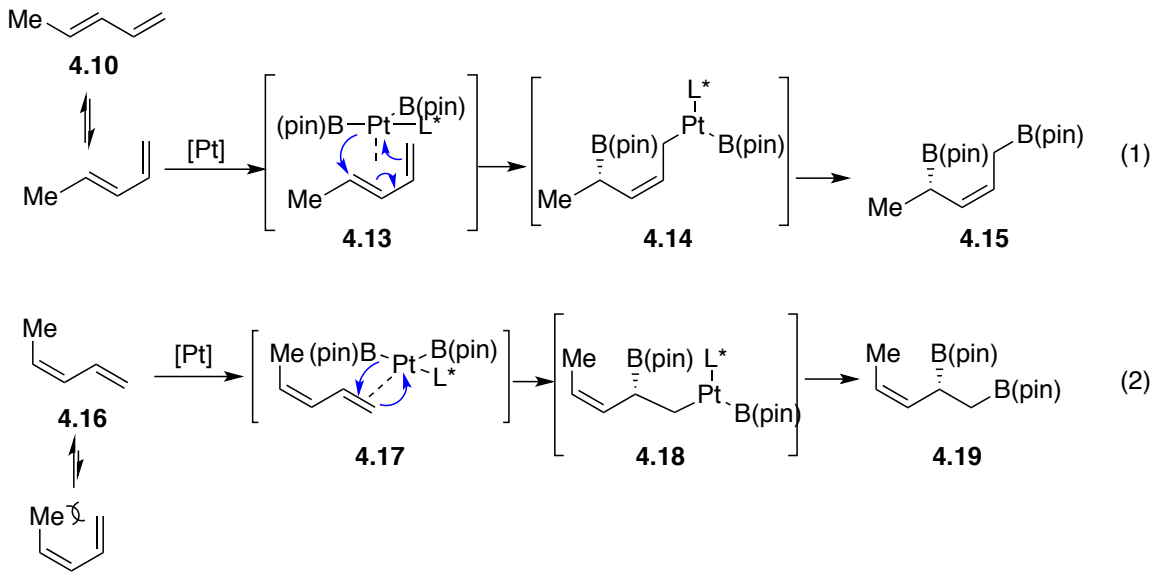



The mechanism for the platinum-catalyzed 1,4-diboration of 1,3-dienes is proposed to proceed via coordination of the diene to a platinum bis(boryl) complex (**4.13**, Scheme 4.6, eq. 1) with the diene in the S-cis conformation. After a 1,4-migratory insertion, an $\eta^1$-allylPt(II) intermediate **4.14** is obtained. Reductive elimination occurs from the least hindered site yielding the 1,4-addition adduct **4.15**.[23] In the case of the cis-1,3-diene substrates, the 1,2-diboration is thought to be favored because the substrate

[22] Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Ang. Chem. Int. Ed*. **2012**, *51*, 521.
[23] (a) Hughes, R. P.; Powell, J. *J. Am. Chem. Soc.* **1972***, 94*, 7723. (b) Hughes, R. P.; Powell, J. *J. Organometal. Chem.* **1972**, *34*, C51.

cannot adopt the S-cis conformation necessary for the 1,4-migratory insertion, due to $A^{1,3}$ strain. Instead, the cis-diene will react in the S-trans conformation and proceed through a 1,2-migratory insertion mechanism, and after reductive elimination, yield the 1,2-diboration product (Scheme 4.6, eq. 2).

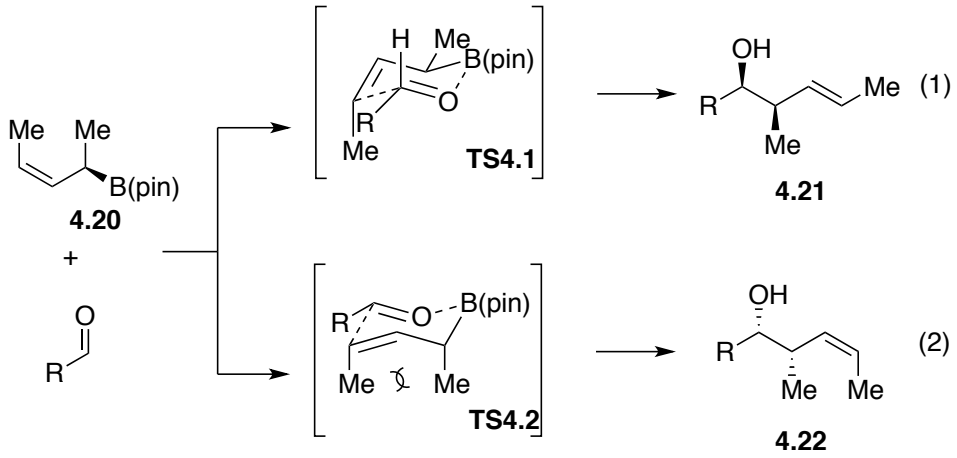
**Scheme 4.6: Mecahnistic Propoasal for Regiochemcial Outcome of Asymmetric Diboration of Dienes**




Enantioenriched α-substituted allylboronates have been shown by Hoffman and co-workers to proceed in allylation reactions with high levels of chirality transfer.[24] There are two possible transition states for the allylation (Scheme 4.7), and these reactions have been shown to proceed exclusively *via* transition state **TS4.1**, which avoids $A^{1,3}$ strain between the cis-olefin substituent and the substituent at the stereocenter.

[24] (a) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123. (b) Hoffmann, R. W.; Neil, G.; Schlapbach, A. *Pure Appl. Chem*. **1990**, *62*, 1993. (c) Andersen, M. W.; Hidlebrndt, B.; Kosher, G.; Hoffman, R. W. *Chem. Ber.* **1989**, *122*, 1777.

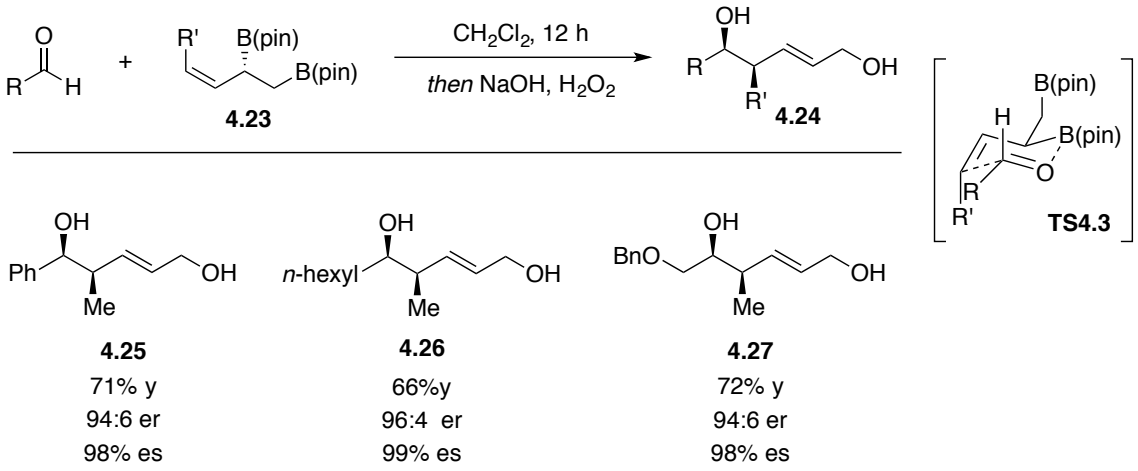
**Scheme 4.7: Transition States for Allylation of Aldehydes with Enantioenriched α-Substituted Allylboronates**




Since the above described asymmetric 1,2-diboration of 1,3-dienes results in similar enantioenriched α-substituted allylboronates, these motifs should undergo similar allylations with carbonyl compounds with high chirality transfer. This is the case as demonstrated by Morken and co-workers, in which 1,2-bisboronates of type **4.23**, proceed in allylation reactions with aliphatic, aromatic and α,β-unsaturated aldehydes in high yields and enantiospecificities (Table 4.1) *via* **TS4.3**.[25]

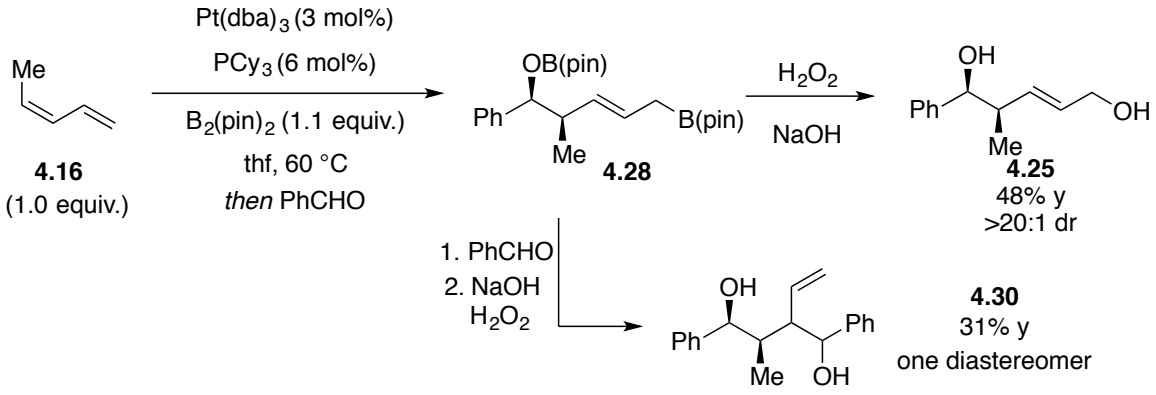
[25] Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem. Int. Ed.*, *51*, 521.

**Table 4.1: Selected Examples of Stereoselective Allylatiom with 1,2-BIs(boronate)esters**




During the development of this one pot-diboration/allylation method, the authors observed competitive double allylation with monosubstituted dienes such as cis-1,5-pentadiene **4.16**. The first allylation results in a second allylboronate **4.28**, which can also participate in a subsequent allylation to give product **4.30** (Scheme 4.8). However, if a 3,3-disubstituted diene is used, the second allylation is prevented due to the steric hindrance caused by the quaternary center at the reactive carbon.

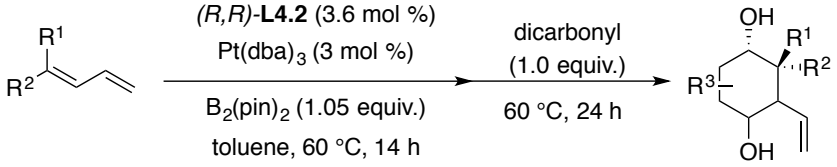
**Scheme 4.8: Overallylation of Aldehydes with 1,2-BIs(boronate)esters**

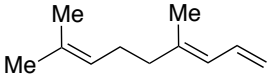
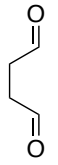
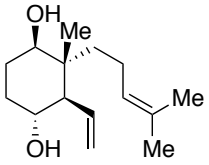
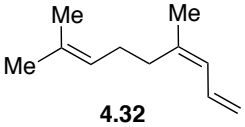
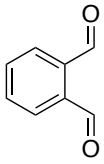
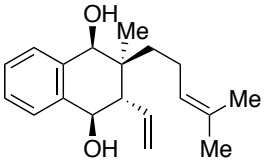
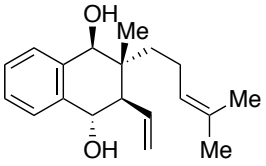
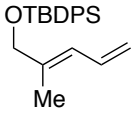
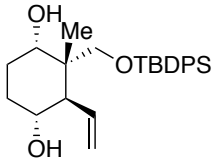
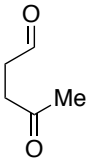
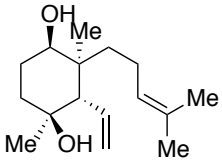
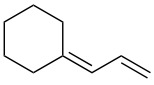
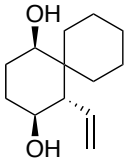


Morken and co-workers were later able to take advantage of this double allylation.[26] If the flask is charged with a 1,4-dicarbonyl, rather than a monoaldehyde, a double allylation can take place and lead to the construction of useful 1,4-cyclohexanediols in high yield, diastereo- and enantioselectivities (Table 4.2). In the examples shown, the diastereoselectivity refers to the alcohol stereocenters as cis or trans with the major product shown. An interesting feature of the reaction is that nonsymmetric carbonyls will react selectively (Table 4.2, entry 6), where the first allylation occurs at the least hindered site.

[26] Ferris, G. E.; Hong, K.; Roundtree, I. A.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, 135, 2501.

**Table 4.2: Selected Examples of Tandem Diene Diboration/Double Allylation of Dicarbonyls**



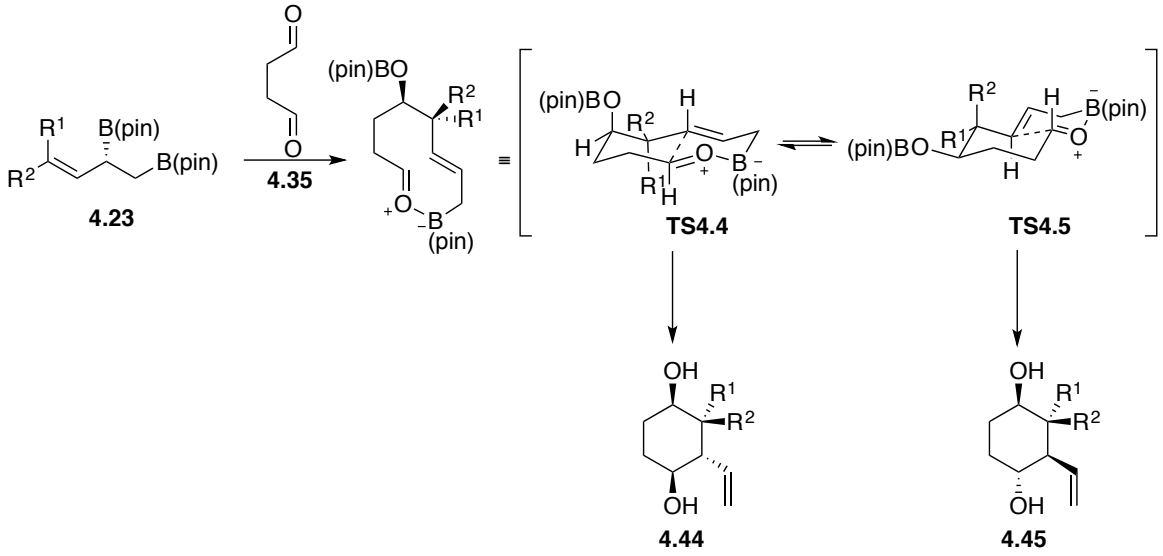

| entry | diene | electrophile | product | dr[a] | er[b] | yield[c] |
|---|---|---|---|---|---|---|
| 1[d] |  **4.31** |  **4.35** |  **4.38** | 5:1 | 96:4 | 76% |
| 2 |  **4.32** |  **4.36** |  **4.39** | 2.8:1 | 96:4 | 83% |
| 3 | **4.31** | **4.36** |  **4.40** | 1.2:1 | 97:3 | 72% |
| 4[d,e] |  **4.33** | **4.35** |  **4.41** | 10:1 | 97:3 | 71% |
| 5 | **4.32** |  **4.37** |  **4.42** | 11:1 | 97:3 | 77% |
| 6 |  **4.34** | **4.35** |  **4.43** | 9:1 | 88:12 | 72% |

[a] diastereoselectivity was determined by $^1$H-NMR analysis. [b]enantioselectivity was deteremined by SFC on chiral stationary phase. [c]yield represents the yield of the isolate mixture of diastereomer. [d] 2.0 equiv. of dialdehyde was used. [e] *(S,S)*-**L4.2** used for this experiment.

The stereochemical outcome of the second allylation reaction can be rationalized through a *trans*-decalin type transition-state (Scheme 4.9). The product of the reaction involving **4.34** (Table 4.2, entry 6) where both R groups are the same, indicates that the OB(pin) prefers to sit in the axial position and procced through **TS4.4** to yield the 1,4-*syn*-product **4.44** (Scheme 4.9).[27] When $R^2$>$R^1$, the reaction will procced through **TS4.4** since the $R^2$ is in the favored equatorial position (Table 4.2, entry 2, 4, 5, 6). The selectivity switches when $R^1$>$R^2$, now the preference to put the R1 group equatorial overrides the preference for the OB(pin) to sit axial, proceeding through **TS4.5**, resulting in the 1,4-*anti*-product **4.45** (Table 4.2, entry 1, 3).

[27] For references showing preference for axial oxygen groups on cyclohexanones see: Baghdasarian, G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 6851. (b) Dibble, D. J.; Ziller, J. A.; Woerpel, K. A. *J. Org. Chem.* **2011**, *76*, 7706. (c) Freitas, M. P.; Tormena, C. F.; Olivira, P. R.; Rittner, R. *J. Mol. Struc. (Theochem)* **2002**, *589-590*, 147. (d) Takahashi, O.; Yamasaki, K.; Kohno, Y.; Ueda, K.; Suezawa, H.; Nishio, M. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 272. (e) Kihara, M.; Iwai, Y.; Nagao, Y. *Hetereocycles* **1995**, *41*, 2279. (f) Nagao, Y.; Goto, M. *Hetereocycles* **1995**, *41*, 883.

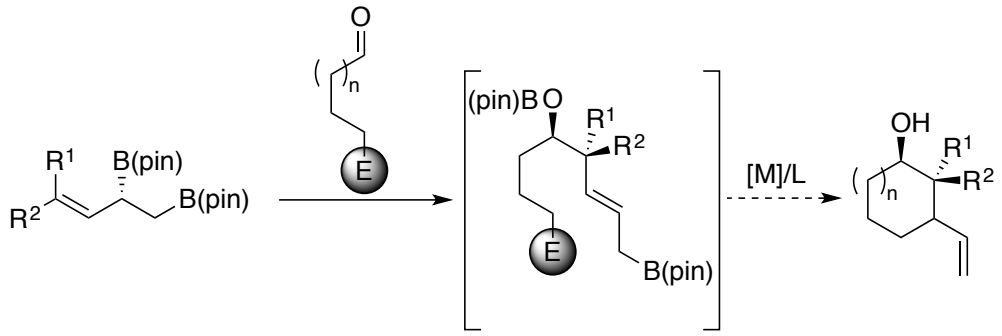
**Scheme 4.9: Transistion State Models for Stereoinduction in Double Allylation**




The tandem diene diboration/double allylation of dicarbonyls is a fairly broad method for the construction of enantioenriched cyclohexanols; however, when attempting to expand the scope of the reaction to form 7-membered ring systems with 1,5-dicarbonyls, the reaction failed. The authors observed a complex mixture of products, as well as monoallylation products.[28] Though the double alllylation method has yet to be expanded to larger ring systems, we imagined that closing the ring with a different type of reaction could allow for a more general method. Aside from allylations of carbonyl compounds, allyl boronates can also be used in metal-catalyzed cross-coupling reactions. It was considered that employing a cross-coupling reaction to close the ring with a different electrophile could allow for a broader scope (Scheme 4.10).

[28] Ferris, G. E. Platinum-Catalyzed 1,2-Diboration of Cis-Substituted 1,3-Dienes: A Route to Enantioenriched Bifunctional Allylboration Reagents. Ph. D. Dissertation, Boston College, Chestnuthill, MA, 2013, pg 190.

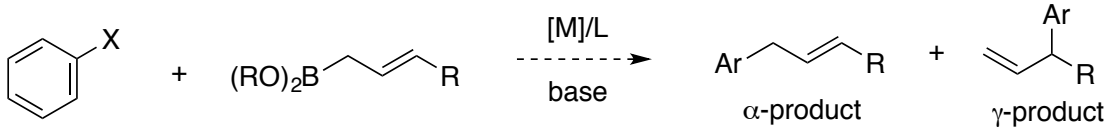
**Scheme 4.10: Proposed Ring-Closure with Different Bis(electrophiles)**




### *4.2.2 Pd-Catalyzed Cross-Coupling Reactions with Allylboronic Ester Nucleophiles*

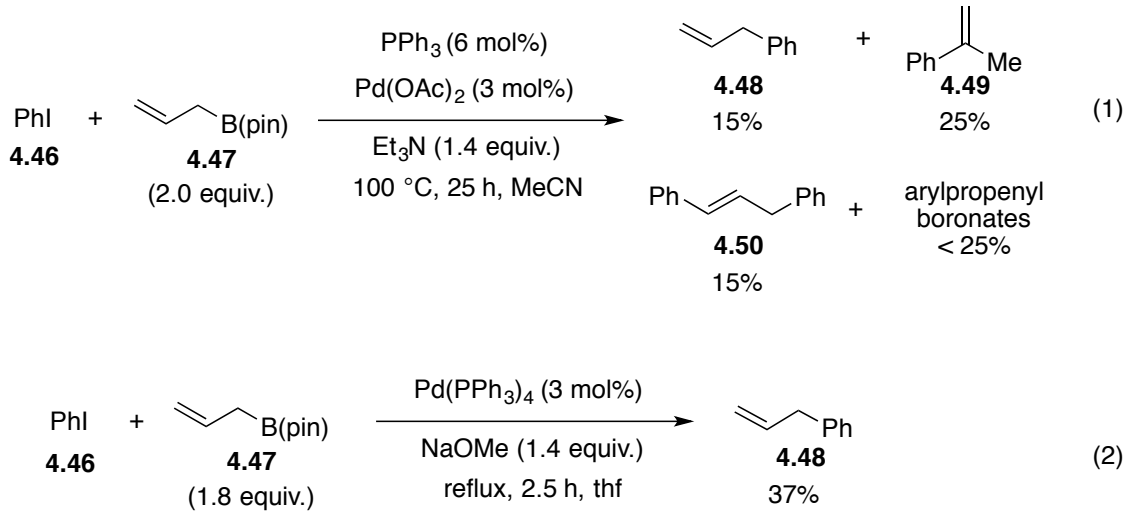
Pd-catalyzed Suzuki cross-coupling reactions are prevalent in the context of synthesis, due to the ability to easily form new carbon-carbon bonds from stable organoboronates with high functional group tolerance. However, allylboronic esters have found less use as nucleophiles in these processes due to difficulties in controlling the regiochemical outcome of the reaction. Nonsymmetric allylboron reagents can cross-couple at either the $\alpha$- or $\gamma$-sites of the nucleophile (Scheme 4.11). In some cases, with the right combination of ligand, base, and reaction conditions a regioselective reaction can be realized.

**Scheme 4.11: Possible Regioisomers Formed in Allyl-Aryl Cross-Coupling**



The earliest example of employing allylboronates in cross-coupling was presented by Hallberg and co-workers in 1987.[29] With the aim of expanding the scope of Heck type-coupling to include allylboronate esters, the authors discovered that cross-coupling could take place favorably over the Heck pathway. Treatment of allylboronate ester **4.1** with iodobenzene in the presence of triethyl amine, palladium acetate and triphenylphosphine gave a mixture of products with a small amount of allyl benzene (Scheme 4.12, eq. 1). After further optimization it was found that the use of sodium methoxide as the base and $Pd(PPh_3)_4$ as the catalyst gave the allyl-aryl cross-coupling exclusively (Scheme 4.12, eq. 2).

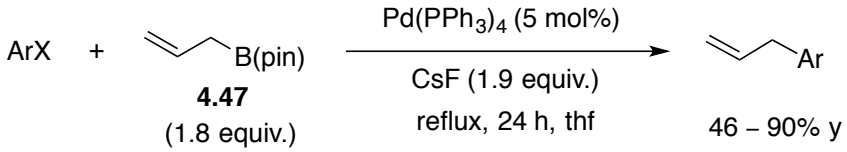
**Scheme 4.12: Development of Intermolecular Allyl-Aryl Cross-Coupling by Hallberg and Co-workers**




[29] Nilsson, K.; Hallberg, A. *Acta. Chemica. Scand.* **1987**, *41*, 569.

It was almost 20 years before allylboron nucleophiles would begin to see use again as nucleophiles in cross-coupling reactions. Kotha disclosed improvements upon the method developed by Hallberg in 2005.[30] Employing a range of aryl iodides and bromides with **4.47**, $Pd(PPh_3)_4$ as the catalyst and CsF as the base under refluxing conditions, allylated arenes were obtained in moderate to high yields (Scheme 4.13). They note that CsF as the base seems to be crucial for the coupling reaction.

**Scheme 4.13: Optimized σ-Selective Allyl-Aryl Cross-Coupling by Kotha and Co-workers**

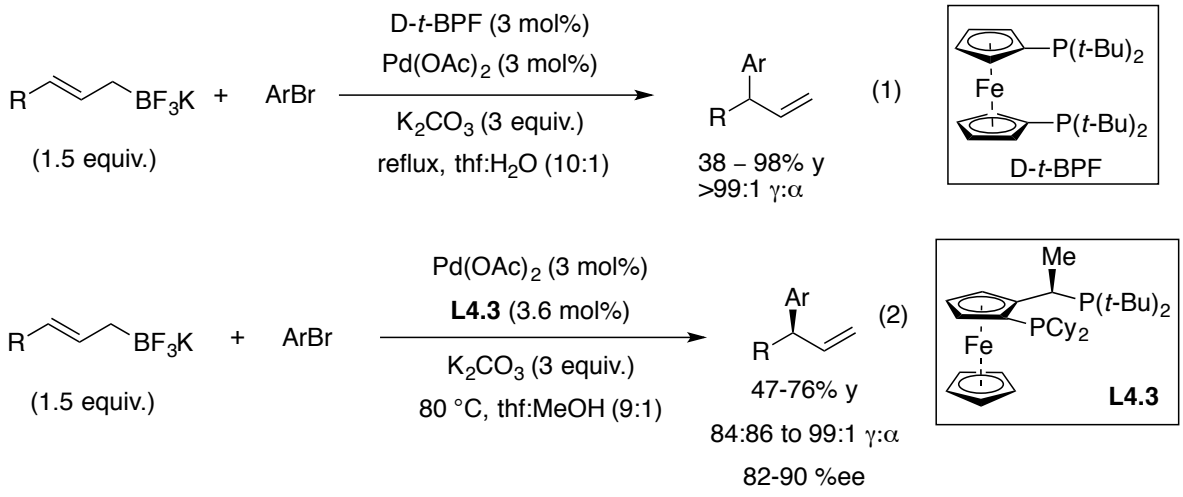



Substituted allylboronic acids also started seeing use at this time in regiocontrolled cross-coupling reactions. Miyaura and co-workers presented a γ-selective cross-coupling of allyltrifluoroborates and aryl electrophiles (Scheme 4.14, eq. 1).[31] After a ligand investigation it was found that wider bite angle ligands such as dppp and dppf gave the highest γ/α-product ratios. More electron-rich ligands gave the highest yields, leading to D-*t*-BPF as the optimal ligand. The authors proposed that electron-rich ligands avoid β-hydride elimination byproducts by facilitating faster reductive elimination. Later this group was able to develop an asymmetric variant of the

[30] Kotha, S.; Behera, M.; Shah, V. R. *Syn. Lett.,* **2005**, *12*, 1877.
[31] Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett., **2006**, 35*, 704.

intermolecular allyl-aryl cross-coupling, the only method to date which uses allyl boron nucleophiles for this transformation (Scheme 4.14, eq. 2.)[32]

**Scheme 4.14: γ-Selective Intermolecular Allyl-Aryl Cross-Coupling by Miyaura and Co-workers.**



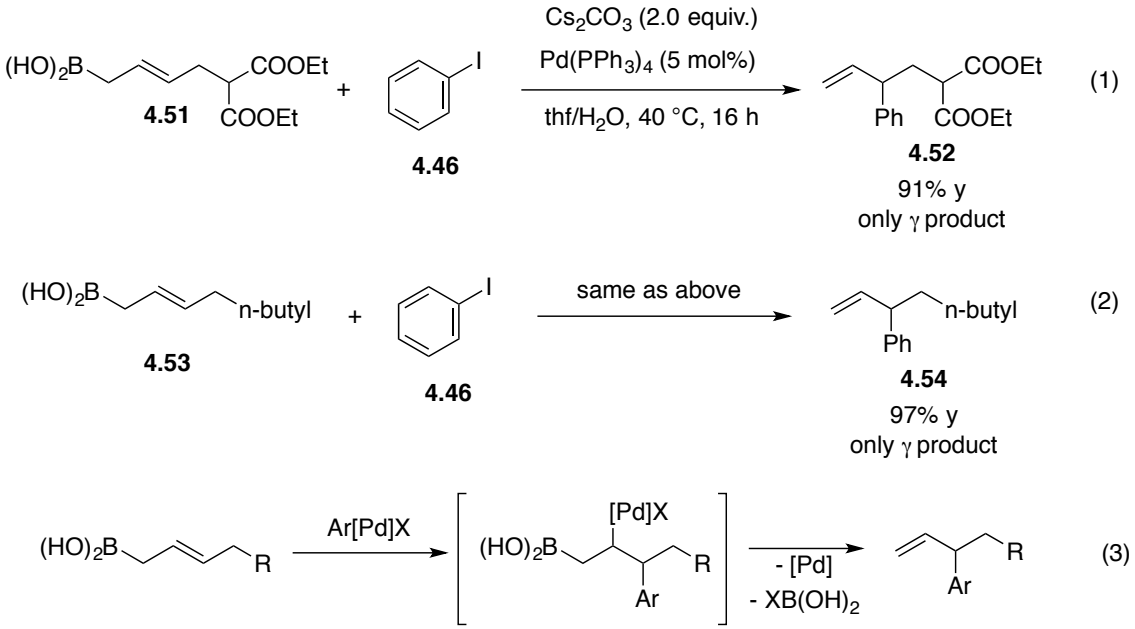

In the same year, another γ-selective cross-coupling of allylboronic acids was disclosed by Szabo,[33] however, the authors in this case propose a distinct mechanism that leads to the observed regioselectivty. In traditional allylic substitution reactions, with allylic electrophiles, the reaction proceeds through an ($\eta^3$-allyl)palladium intermediate in which an outersphere attack of a nucleophile occurs at the less hindered carbon.[34] These outersphere attacks almost always lead to linear products unless

[32] Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.,* ***2006****, 35*, 1368.
[33] Sebelius, S.; Olsson, V.; Wallner, O. A.; Szabo, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 8150.
[34] For select examples of an outersphere mechanism in Pd-allyl cross-coupling see:(a) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343. (b) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2007**, *129*, 11876.

directing groups are used.[35] In this case, internal allylic boronic acids are cross-coupled with aryl iodides in the presence of a Pd(0) catalyst (Scheme 4.15). Initially one could consider that the diester moiety in substrate **4.51** (Scheme 4.15, eq. 1) could direct the reaction, however even with the alkyl-substituted nucleophile **4.53** (Scheme 15, eq. 2) only the branched isomer is observed. The authors propose that the reaction does not proceed via a ($\eta^3$-allyl)palladium intermediate, but rather after oxidative addition of the aryl halide a regioselective carbopalladation occurs, followed by $\beta$-boryl elimination to yield the desired product (Scheme 4.15, eq. 3).

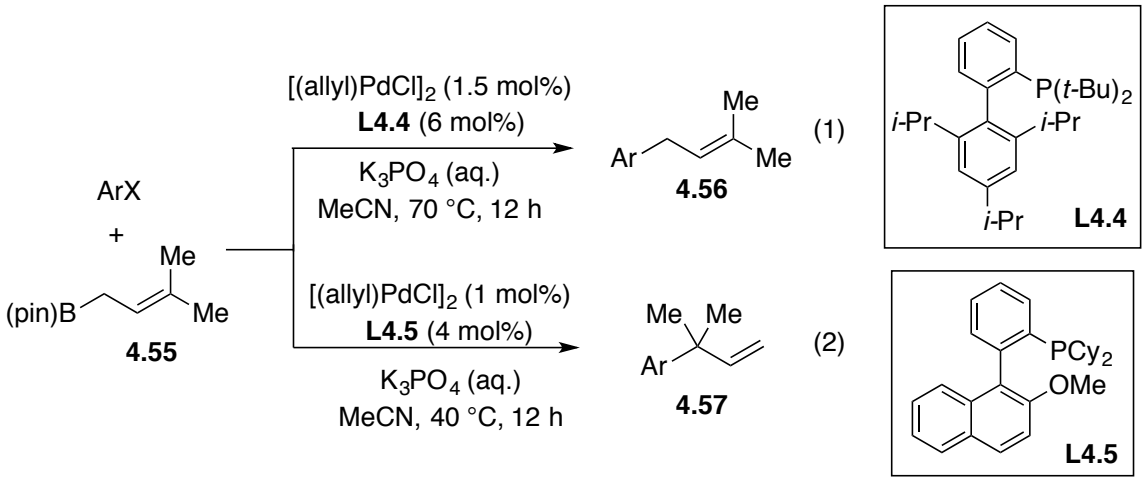
[35] (a) Cook, G. R.; Yu, H.; Sankaranarayan, S.; Shanker, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 5115. (b) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **1999**, *121*, 4545. (d) Itami, K.; Koike, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2001**, *123*, 6957. (e) Krafft, M. E.; Sugiura, M.; Abboud, K. A. *J. Am. Chem. Soc.* **2001**, *121*, 9174.

**Scheme 4.15: Mechanistic Insights into Allyl-Aryl Cross-Coupling by Szabo and Co-workers**




In 2013, Buchwald discovered an orthogonal set of catalyst systems that could selectively give either the $\gamma$ or $\alpha$ product depending on the ligand employed. Cross-coupling of boronic ester **4.55** and aryl halides with a palladium catalyst and a sterically demanding ligand such as tBuXPhos (**L4.4**) led to formation of the $\alpha$-product, while a less sterically demanding ligand **L4.5** led to formation of the $\gamma$-product (Scheme 4.16, eq. 1). The authors indicate that further experimentation to determine the origin of the regiochemical outcomes for the different ligand sets are ongoing.

**Scheme 4.16: Regiodivergent Allyl-Aryl Cross-Coupling by Buchwald and Co-workers**



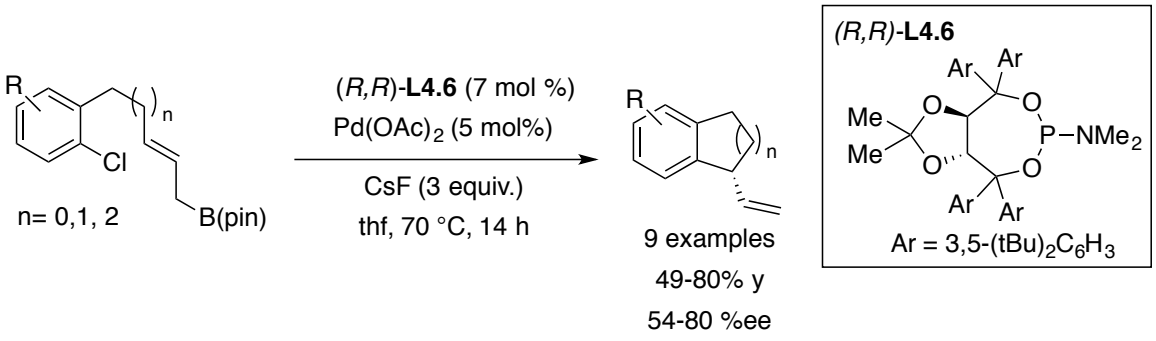

All of the examples thus far have focused on the intermolecular cross-coupling of C($sp^2$) electrophiles with allylboron nucleophiles. There are several examples of intramolecular variants of this type of coupling with allylsilanes[36], and allylstannanes;[37] however, there is only one example empoying allylboron nucleophiles. In 2014, Morken and co-workers described an asymmetric intramolecular allyl-aryl cross-coupling to furnish enantioenriched carbocycles.[38] Allylboronic pincol esters tethered to aryl halides undergo efficient cross-coupling with a palladium catalyst and chiral monodentate phosphine ligand (**L4.6**) with CsF as the base (Scheme 4.17). This method can furnish 5-, 6-, and 7-membered ring systems in moderate yield and enantioselectivities.

[36] (a) Tietze, L. F.; Schimpf, R. *Angew. Chem. Int. Ed.* **1994**, *33*, 1089. (b) Tietze, L. F.; Thede, K.; Schimpf, R.; Sannicoló, F. *Chem. Commun*. **2000**, *583*. (c) Tietze, L. F.; Modi, A. *Eur. J. Org. Chem.* **2000**, 1959.

[37] (a) Trost, B. M.; Walchi, R. *J. Am. Chem. Soc.* **1987**, *109*, 3487. (b) Grigg, R.; Sansano, J. M. J. *Tetrahedron* **1996**, *52*, 13441.

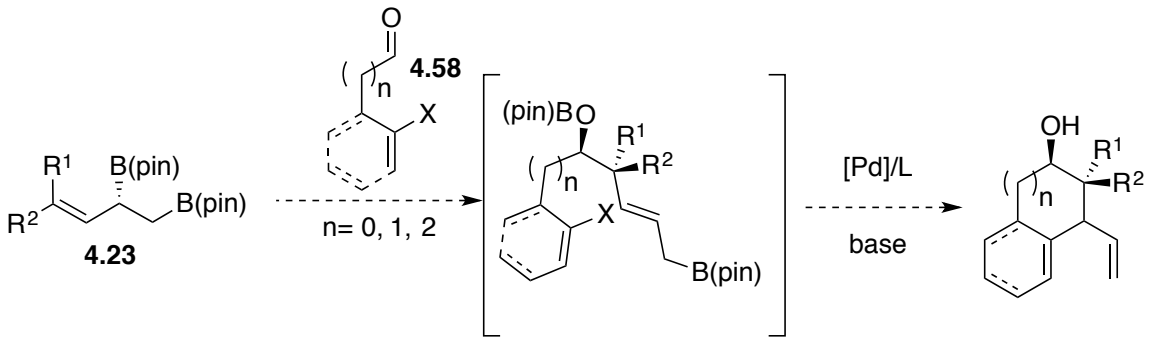
[38] Schuster, C. H.; Coombs, J. R.; Kasun, Z. A.; Morken, J. P. *Org. Lett.* **2014**, *16*, 4420.

**Scheme 4.17: Asymmetric Intramolecular Allyl-Aryl Cross-Coupling by Morken and Co-workers**




The above described examples indicate that a similar palladium-catalyzed intramolecular cross-coupling could likely be applied in a tandem reaction to close different sized ring systems. We propose that after asymmetric diboration of 1,3-dienes, allylation with electrophiles of type **4.58** (Scheme 4.18), followed by a diastereoselective palladium-catalyzed cross-coupling, could furnish the desired ring systems.

**Scheme 4.18: Proposed Asymmetric Diboration/Allylation/Cross-Coupling**



## 4.3 Development of One Pot, Diboration Allylation Cross-Coupling[39]

The proposed asymmetric diboration/allylation/cross-coupling (DACC) would allow one to quickly build up complexity from readily available dienes. The proposed products of the method would map on to a number of structurally diverse terpenoid natural products (Scheme 4.19)[40], which can be used as medicines, fragrances, and hormones.[41] Cyclic terpenoids have classically been synthesized through carbocyclizations[42] and cycloaddition reactions[43], this method could offer an alternative to these approaches and perhaps more readily allow for synthesis of derivatives of these scaffolds.

[39] Shields, J. D.; Eno, M. S.; Chang, W. K.; Morken, J. P. *Manuscript in Prep*. **2017**

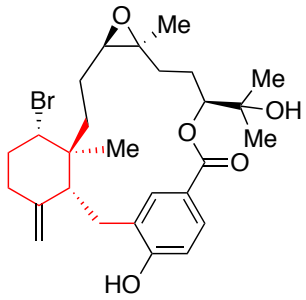
[40] (a) Kubanek, J.; Prusak, A. C.; Snell, T. W.; Ciese, R. A.; Fairchild, C. R.; Aalbersberg, W.; Hay, M. E. *J. Nat. Prod.* **2006**, *69*, 731. (b) Meng, Z.; Yu, H; Li, L.; Tao, W.; Chen, H.; Wan, M.; Yang, P.; Edmonds, D. J.; Zhong, J.; Li, A. *Nature Comm.* **2015**, *6*, 6096. (c)Wu, Z.-J.; Xu, X.-K.; Zeng, H.-W.; Shen, Y.-H.; Tian, J-M.; Su, J.; Li, H.-L.; Shan, L.; Liu, R.-H.; Zhang, W.-D. *Planta Med.* **2011**, *77*, 1545. (d) Ly, G.; Knorre, A.; Schmidt, T. J.; Pahl, H. L.; Merfort, I. *J. Biol. Chem.* **1998**, *273*, 33508. (e) Reiner, G. C.; Katzenelenbogen, B. S.; Bindal, R. D. *Cancer Res.* **1984**, *44*, 2302.

[41] Breitmaier, E. *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones* (Wiley-VCH, Weinheim, Germany, 2006.)

[42] Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.

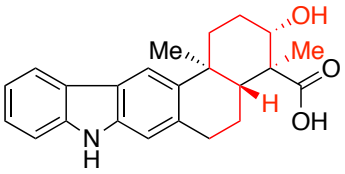
[43] (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668. (b) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003.

**Scheme 4.19: Selected Examples of Terpenoid Natural Products**[40]



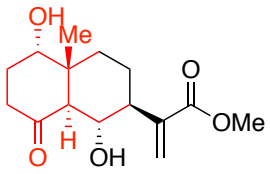

*bromophycolide F*[a]

**4.59**



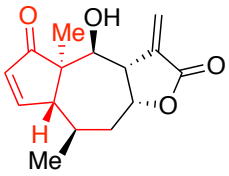

*xaimycin A*[b]

**4.60**



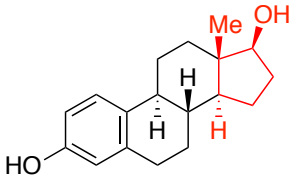

*ainsliatone B*[c]

**4.61**



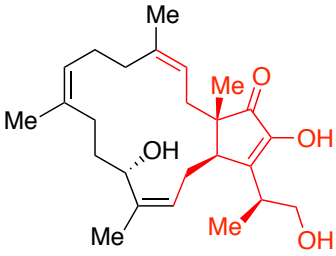

helenalin[d]

**4.62**




estradiol[e]

**4.63**



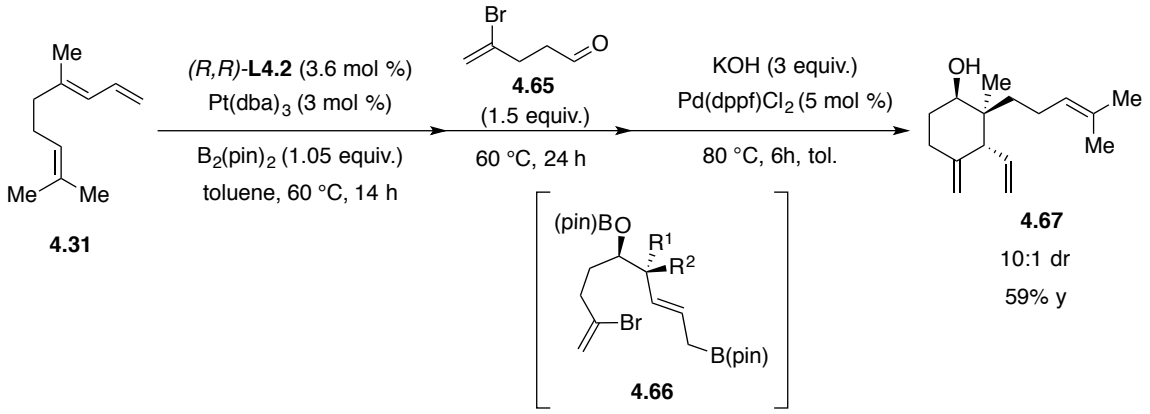

terpestacin[f]

**4.64**

### *4.3.1. Development of DACC to Form Six-Membered Rings*

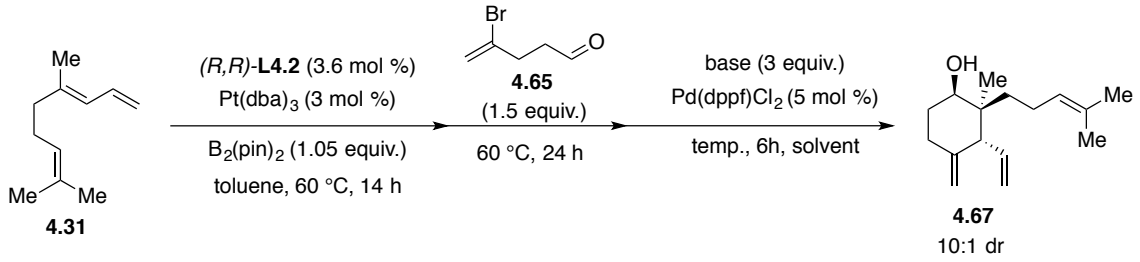
We began our reaction development by conducting the DACC sequence with geraniol-derived diene **4.31** and aldehyde **4.65** (Scheme 4.20), expecting to form a six membered-ring upon cross-coupling. A small catalyst screen showed that the use of Pd(dppf)$Cl_2$ with potassium hydroxide as the base gave the desired product as the only regioisomer, in good yield and high diastereoselectivity. The diastereoselectivity in this chapter will refer to the relationship between the vinyl group and the hydroxyl, as the quaternary center is set through a highly selective allylation (>20:1 dr).

**Scheme 4.20: Initial Result for DACC to Form Cyclohexenols**




To increase the yield of the reaction, different temperatures, solvents and bases were investigated (Table 4.3). Decreasing the temperature of the reaction did not improve the yield of the desired product and led to incomplete conversion of intermediate **4.66** (entry 2, 3). Reaction in tetrahydrofuran occurred similarly, while in 1,4-dioxane only trace amount of the desired product was formed (entry 4, 5). Employing a weaker base such as CsF led to a complex mixture (entry 7) with only trace product detected. It seemed that the initial conditions of KOH in toluene at 80 °C led to the highest isolated yields of the desired product. At this point we decided to test conditions with a different dielectrophile to form 5-membered rings.

**Table 4.3: Screening of Conditions for DACC for Cyclohexenols**

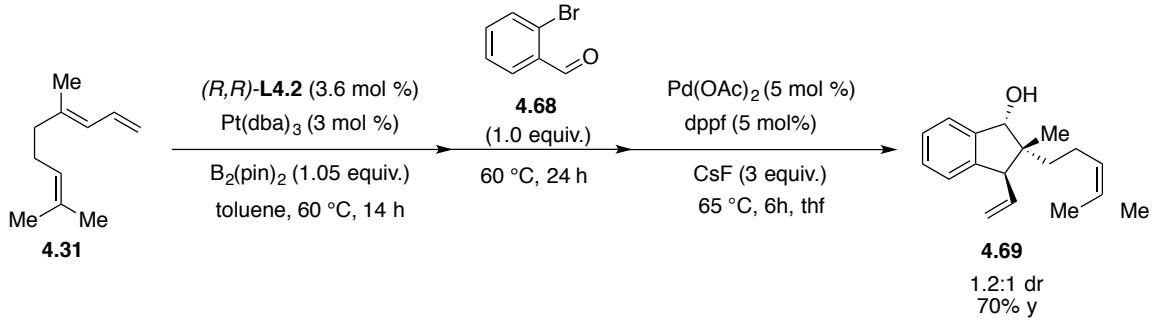



| entry | base | solvent | temp. | isolated yield |
|---|---|---|---|---|
| 1 | KOH | toluene | 80°C | 59% |
| 2 | KOH | toluene | 60°C | 40% |
| 3 | KOH | toluene | 40°C | 30% |
| 4 | KOH | THF | 60°C | 53% |
| 5 | KOH | 1,4-dioxane | 60°C | trace |
| 6 | NaOH | THF | 60°C | 51% |
| 7 | CsF | THF | 60°C | trace |

### *4.3.2. Development of DACC to Form Five-Membered Rings*

When changing the electrophile to 2-bromobenzaldehyde **4.68**, significant amounts of protodeboronation was observed, along with low diastereoselectivity slightly favoring the anti-configuration. Switching to cesium fluoride, an anhydrous weak base that might avoid protodeboronation, improved the yield but the diastereoselectivity remained low (Scheme 4.21).

**Scheme 4.21: Initial Result for DACC to Form Cyclopentenols**

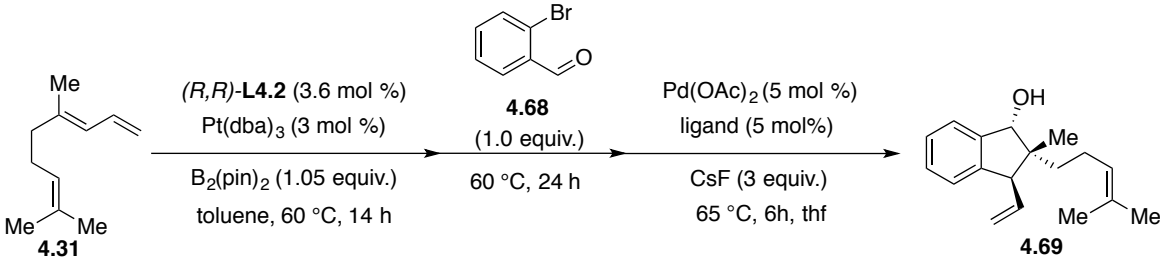



We predicted that changes in the ligand structure could influence the diastereoselectivity of the reaction and therefore screened several bidentate and monodentate ligands (Table 4.4). Since the reaction sequence is a one-pot operation, we needed to learn if the *(R,R)*-**L4.2** ligand from the asymmetric diboration step was influencing the selectivity of the cross-coupling step. Thus, with $Pd(OAc)_2$ and no exogenous ligand, the cross-coupling step did not proceed (entry 1). Next the effect of the exogenous ligands were studied. Increasing the steric bulk of the bidentate ligand only improved the diastereoselectivity slightly (entry 2, 3), and simple monodentate phosphine ligands failed to increase the selectivity to synthetically useful levels (entry 4, 5). Improvements in diastereoselectivity were not observed until biaryl Buchwald-type ligands were employed. [44] These ligands offer unique interactions with the palladium. During oxidative addition the ligand can behave as a monodentate ligand, increasing the rate of the oxidative addition. After oxidative addition, the metal can form an interaction

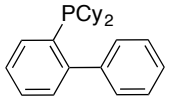
[44] (a) Surry, D. S. and Buchwald, S. L. *Chem. Sci.,* **2011**, *2*, 27. (b) Martin, R. and Buchwald, S. L. *Acct. Chem. Res.,* **2008**, *41*, 1461. (c) . Surry, D. S. and Buchwald, S. L. *Agnew. Chem. Int. Ed.,* **2008**, *47*, 6338.

with the *ipso*-carbon of the bottom aromatic ring, promoting reductive elimination.[45] More sterically encumbered ligands XPhos and RuPhos resulted in higher diastereoselectivtiy than JohnPhos (entry 6, 7, 8), with XPhos giving the highest selectivity at 7:1 dr.

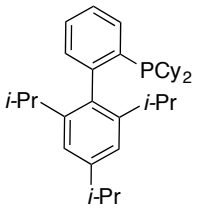
**Table 4.4: Screening of Ligands for DACC for Cyclopentenols**



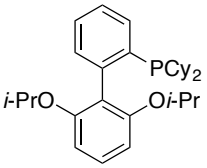

| entry | ligand | dr[a] | isolated yield |
|---|---|---|---|
| 1 | none | -- | < 5% |
| 2 | dppf | 1:1.2 | 52% |
| 3 | D-*t*-BPF | 1.7:1 | 54% |
| 4 | $PCy_3$ | 1.7:1 | 54% |
| 5 | $PPh_3$ | 2:1 | 62% |
| 6 | JohnPhos | 4.5:1 | 48% |
| 7 | XPhos | 7:1 | 69% |
| 8 | RuPhos | 3:1 | 74% |




**JohnPhos**




**XPhos**




**RuPhos**

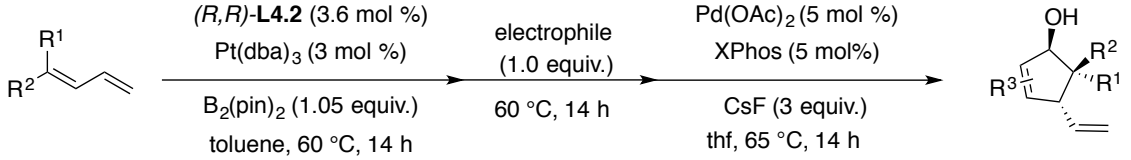
[a] diastereomer ratios were determined by $^1$H-NMR

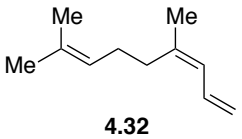
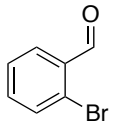
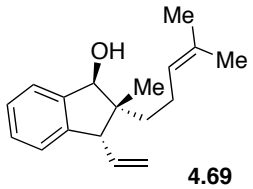
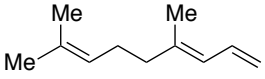
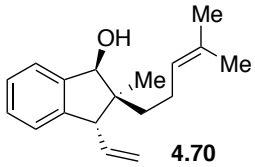
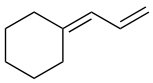
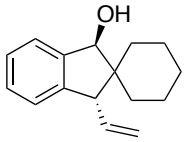
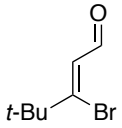
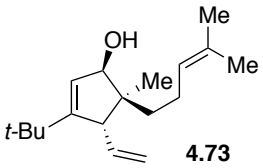
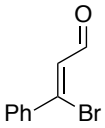
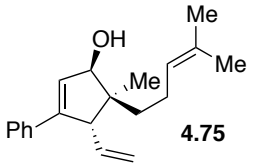
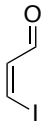
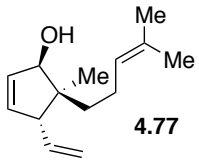
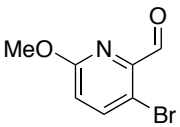
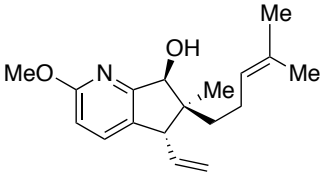
With improved conditions using XPhos as the ligand and CsF as the base, the scope of the intramolecular C(sp2)-allyl cross-coupling to form 5-membered rings was

[45] Cho, E.J.; Senecal, T.D.; Kinzel, T.; Zhang, Y; Watson, D.A.; Buchwald, S.L., *Science*, **2010**, *328*, 167.

investigated (Table 4.5). Changing to nerol-derived diene **4.32**, led to lower diastereoselectivity than the reaction employing the geraniol-derived diene **4.31** (entry 1 vs. 2). We were excited to see that in addition to the aryl electrophiles, alkenyl electrophiles are also competent cross-coupling partners (entry 4-6). We were able to perform the DACC with pyridyl containing electrophile **4.78** (entry 7), obtaining the desired product in high diastereoselectivity and isolated yield.

**Table 4.5:Diboration/Allylation/Cross-Coupling to form Substituted Cyclopentenols**

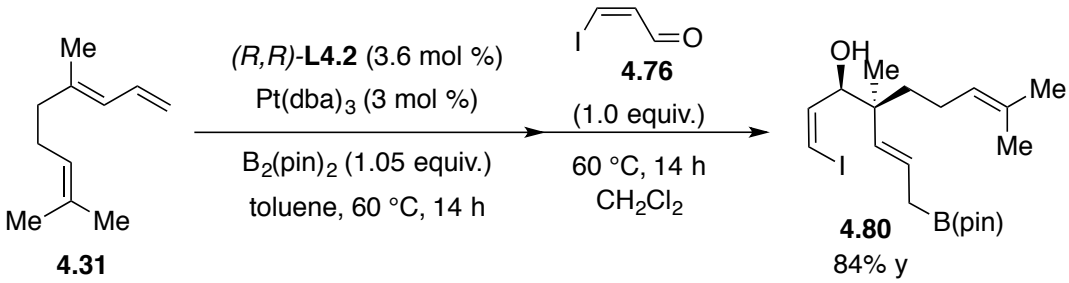



| entry | diene | electrophile | product | dr | yield |
|---|---|---|---|---|---|
| 1 |  **4.32** |  **4.68** |  **4.69** | 1.9:1 | 69% |
| 2 |  **4.31** | **4.68** |  **4.70** | 6.8:1 | 76% y |
| 3 |  **4.34** | **4.68** |  **4.71** | 3.4:1 | 59% y |
| 4 | **4.31** |  **4.72** |  **4.73** | 1.6:1 | 66% y |
| 5 | **4.31** |  **4.74** |  **4.75** | 1.4:1 | 58% y |
| 6 | **4.31** |  **4.76** |  **4.77** | 1.4:1 | 34% y |
| 7 | **4.31** |  **4.78** |  **4.79** | 6.8:1 | 76% y |

Reactions were preformed witih 0.5 mmol of diene. Yields and diastereomer ratios are the average of two experiments. [a] diastereomer ratios were determined by $^1$H-NMR.

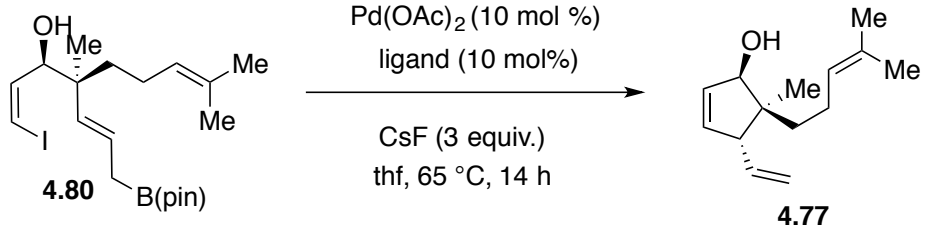
Lower diastereoselectivities were observed in the case of alkenyl electrophiles and diminished yield in the case of iodoaldehyde **4.76** (Table 4.5). Since the scaffold resulting from the DACC with iodoaldehyde **4.76** maps on to steroid type scaffolds, we were interested in increasing the yield and selectivity of this substrate. We decided to optimize further using a two-step procedure. After the asymmetric diboration and allylation the product was isolated and purified by column chromatography to yield allyl boron 4.80 in 84% yield (Scheme 4.22).

**Scheme 4.22: Isolation of Intermediate Allylboronate 4.80**



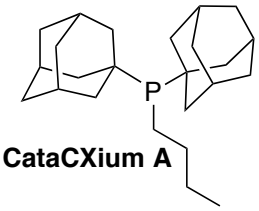

With allyl boronate **4.80** in hand we were able to studied the cross-coupling as an isolated reaction (Table 4.6). During a survey of different ligands, we found that Buchwald-type ligands still lead to lower diastereoselectivities (entry 1-3). Very sterically encumbered monodentate ligands such as CataCXium A and P(*o*-tol)$_3$ (entry 5-8), lead to a surprising reversal in diastereoselectivity now favoring the *syn*-product. Tri(t-butyl)phosphine stood out as the ideal ligand, giving significantly higher selectivies and yields.

**Table 4.6: Optimization of Intramolecular Allyl-Aryl Cross-Coupling**

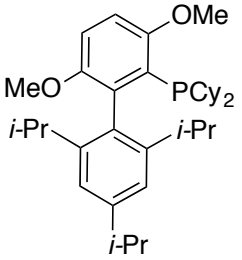



| entry | ligand | dr[a] | $^1$H-NMR yield[b] |
|---|---|---|---|
| 1 | Xphos | 1.8:1 | 23% |
| 2 | *t*-BuXPhos | 1.5:1 | 25% |
| 3 | BrettPhos | 2.6:1 | 17% |
| 4 | P(*t*-Bu)$_3$ | 6.2:1 | 40% |
| 5 | P(*i*-Bu)$_3$ | 1:1.2 | 14% |
| 6 | P(*n*-Bu)$_3$ | 1:1.3 | 11% |
| 7 | P(*o*-tol)$_3$ | 1.2:1 | 14% |
| 8 | CataCXium A | 1:2 | 16% |

[a] diastereomer ratios were determined by $^1$H-NMR.[b] $^1$H-NMR yield measured using 1,3,5-trimethoxybenzene as internal standard.



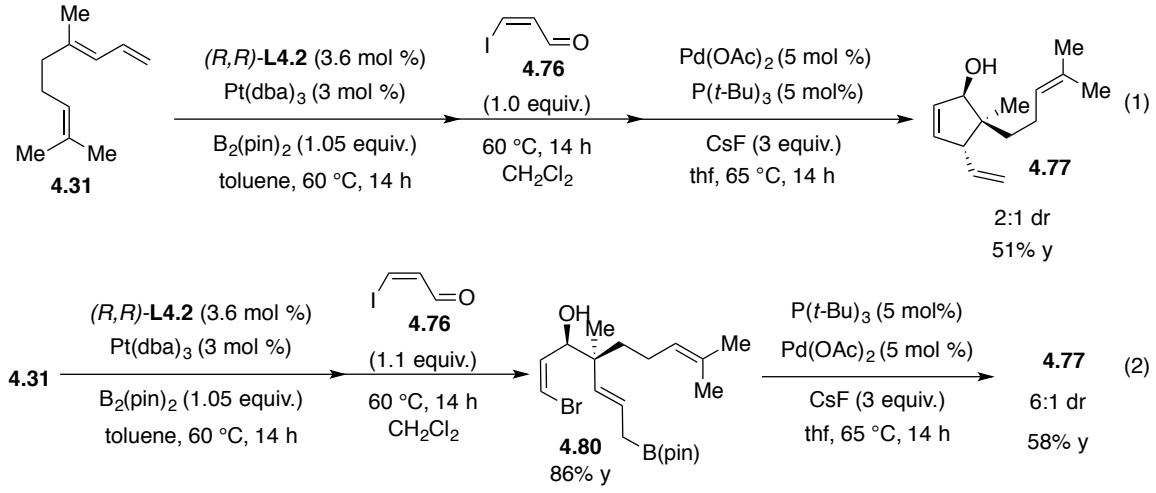

**CataCXium A**




**BrettPhos**

Interestingly when we looked at the one-pot DACC with P(t-Bu)$_3$ as the ligand for the cross-coupling, the diastereoselectivity dropped compared to the two pot procedure (Scheme 23, eq 1 vs 2). We hypothesize that with a larger group on the oxygen B(pin) vs. H in the transition state affects the stereochemical outcome of the reaction. For now, to obtain higher yields and selectivities for this electrophile a two-pot reaction can be performed with P(t-Bu)$_3$.

**Scheme 4.23: Results of One-Pot vs. Two-Pot Diboration/Allylation/Cross-Coupling with P(*t*-Bu)$_3$**



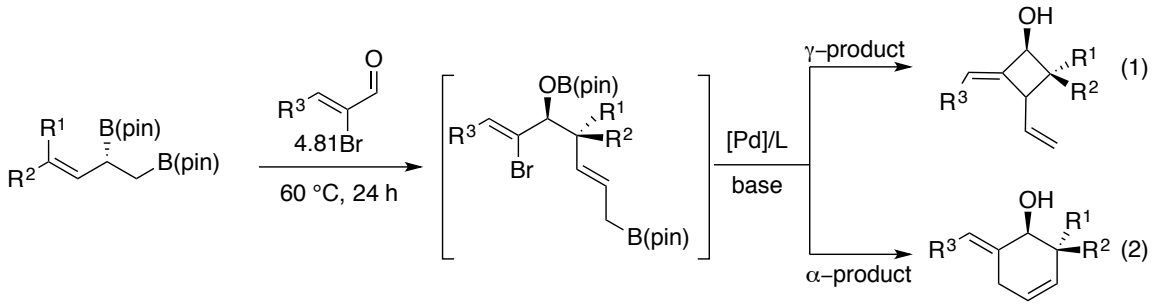

### *4.3.3. Development of* Diboration/Allylation/Cross-Coupling *to Form Cyclobutenols*

Cylcobutane cores are versatile synthetic intermediates: the strain associated with the small ring system allows them to be selectively modified through ring opening, ring expansion and ring contraction reactions.[46] In addition to their use as synthetic intermediates, a number of alkaloids possess cyclobutane cores.[47] There are several classical approaches to the formation of cyclobutane rings, such as [2+2] cycloadditions and ring expansions of cyclopropane.[48] Controlling the enantioselectivity in these types of reactions is often difficult and the development of new metal-catalyzed asymmetric reactions to access these cores would be an important addition to the current synthetic

[46] Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.,* **2003**, *103*, 1485.
[47] Dembitsky, V. D. *J. Nat. Med.* **2008**, *62*, 1.
[48] (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev*. **2010**, *39*, 783. (b) Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, **128**, 7025.

methods.[49] We predicted that by using bromoaldehydes, such as **4.81** that the DACC method could furnish the desired cyclobutenol cores in high yield and stereoselectivity (Scheme 4.24).

**Scheme 4.24: Proposed DACC to form Substituted Cyclobutenols**

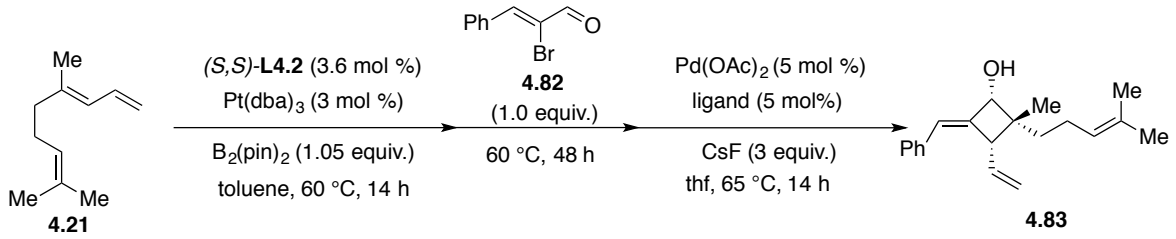



Initial investigation into the DACC with (*Z*)-2-bromo-3-phenylacrylaldehyde **4.82**, revealed that the allylation needed to run for 48 h to give the desired product in highest yields (Table 4.7).This is likely due to the fact that the aldehyde is more sterically encumbered with the $\alpha$-bromide. We were also pleased to see that the desired cyclobutenol was formed selectively with no trace of the $\alpha$-product (Scheme 4.24). It is important to note that unlike the 5- and 6-membered ring derivatives, in this case, the major diastereomer is the *syn*-product (Table 4.7). When looking at the effects of the ligand scaffold on the reaction, like in the 5-membered ring formation electron-rich bidentate ligands lead to low selectivity (Table 4.7, entry 1, 2). We determined that in this

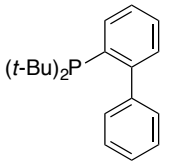
[49] Secci, F.; Frongia, A.; Piras, P. P. *Molecules*, **2013**, *18*, 15541.

case XPhos also gave the highest diastereoselectivites in the reaction, and used this ligand to investigate the scope of the reaction.

**Table 4.7: Screening Ligands for DACC to form Cyclobutenols**




| entry | ligand | dr[a] | isolated yield |
|---|---|---|---|
| 1 | dppf | 1.3:1 | 52% |
| 2 | D-*t*-BPF | 1.7:1 | 54% |
| 3 | $PCy_3$ | 2:1 | 64% |
| 4 | $PPh_3$ | 1.7:1 | 54% |
| 5 | JohnPhos | -- | < 5% |
| 6 | XPhos | 4.7:1 | 65% |
| 7 | RuPhos | 2:1 | 70% |

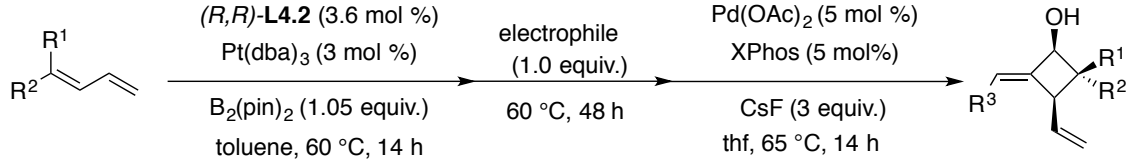


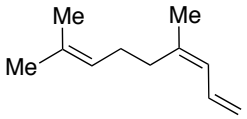
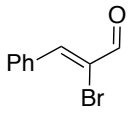
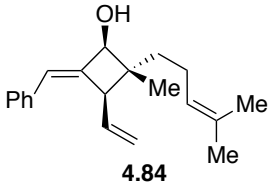
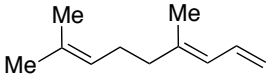
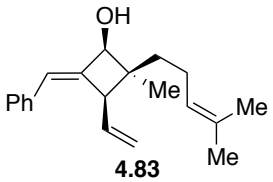
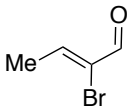
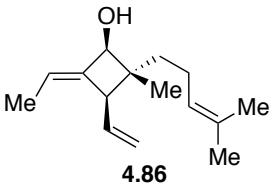
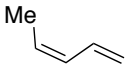
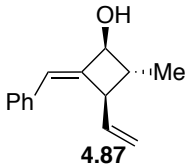

**JohnPhos**

[a] diastereomer ratios were determined by $^1$H-NMR

With optimized conditions in hand, we studied different combinations of coupling partners (Table 4.8). In this case, the nerol-derived diene **4.32**, gave higher diastereoselectivities than the corresponding geraniol-derived diene **4.31** (entry 1 vs 2). The highest diastereoselectivities were observed with mono-substituted diene **4.16**; however, this reaction was performed with 2 equivalents of the diene to prevent over allylation.

**Table 4.8: Diboration/Allylation/Cross-Coupling to form Substituted Cyclobutenols**



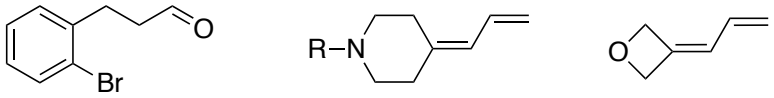

| entry | diene | electrophile | product | dr[a] | yield |
|---|---|---|---|---|---|
| 1 |  **4.32** |  **4.82** |  **4.84** | 7.1:1 | 50% |
| 2 |  **4.31** | **4.82** |  **4.83** | 4.1:1 | 36% |
| 3 | **4.32** |  **4.85** |  **4.86** | 7.8:1 | 62% |
| 4[b] |  **4.16** | **4.82** |  **4.87** | 8.8:1 | 52% |

Reactions were preformed witih 0.5 mmol of diene. Yields and diastereomer ratios are the average of two experiments. [a] diastereomer ratios were determined by $^1$H-NMR. [b] allylation reaction was performed with 0.5 equiv. of aldehyde at room temperature.

*4.3.4. Problematic Coupling Partners*

In efforts to further expand the scope of the DACC, we were interested in employing electrophiles that would furnish 7-membered rings; however, this led to a complex mixture of products under a number of different conditions (Scheme 4.25, **4.88**). Also, dienes containing oxetanes and protected piperidines failed in the asymmetric diboration (Scheme 4.25**, 4.89** and **4.90**).

**Scheme 4.25: Problematic Substrates in DACC**



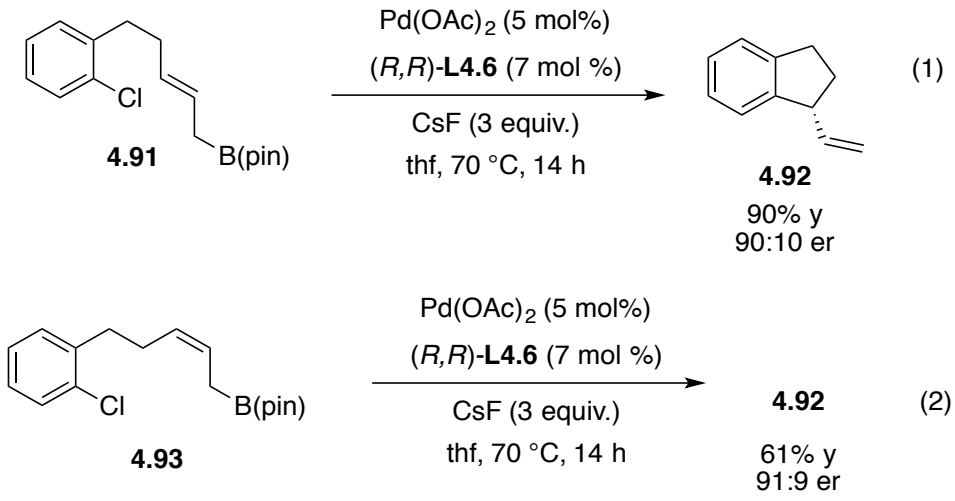

**4.88** **4.89** **4.90**

*4.3.5. Mechanistic Proposal*

To understand the factors that influence the diastereoselectivity we must first determine the mechanism by which the cross-coupling proceeds. Szabo and co-workers proposed that their intermolecular allyl-aryl cross-coupling proceeds through a regioselective carbopalladation, followed by β-boryl elimination to yield the desired product (*vide supra*). However, previous studies in our laboratory on the intramolecular allyl-aryl cross-coupling reveal that this mechanism is likely not operative (Scheme 4.26). In the case of the allyl-aryl cross-coupling, two isomers of the allylboronate were examined; if a carbopalladation were operative, the two different isomers would show a

difference in selectivity. Under the reaction conditions the *(Z)*- and *(E)*-allylic boronates led to the same enantiomer of product, with almost identical levels of enantioselectivity (Scheme 4.26, eq 1 and 2). This supports that instead of a regioselective carbopalladation, the product is formed though the intermediacy of a Pd(II) π-allyl intermediate, which equilibrates to give the more stable diastereomer before reductive elimination.

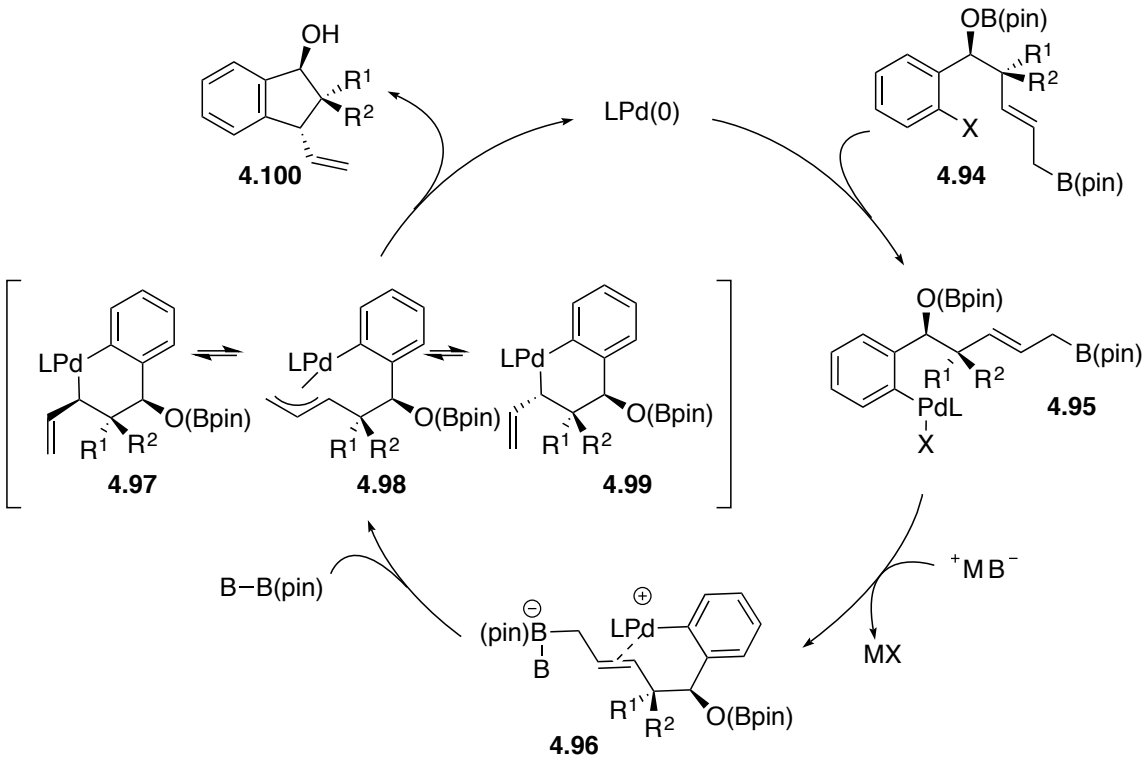
**Scheme 4.26: Examination of Allylboronate Isomers**




We propose that this mechanism is also operative in our system (Scheme 4.27). After oxidative addition to give intermediate **4.95**, activation of the boronate ester with base followed by transmetalation leads to species **4.97-4.99**. These species can interconvert via π-σ-π- isomerization, and then reductive elimination occurs from the more stable diastereomer. However, we cannot rule out the possibility that transmetalation is the stereodefining step, followed by a fast reductive elimination. The specific interactions that lead to one diastereomer over the other is not known at this

time. Since we observe significant differences in outcomes based on the ligand scaffold furnishing different ring sizes, it is difficult to determine which factors lead to formation of one isomer over the other, without further experimentation.

**Scheme 4.27: Proposed Mechanism Cross-Coupling of DACC**




## 4.4 Progress Towards the Total Synthesis of Bromophycolide F

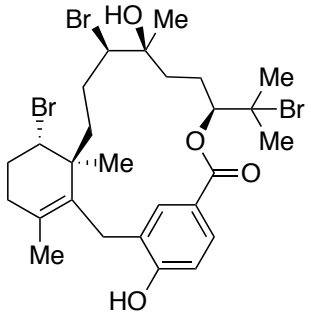
### *4.4.1. Background and Isolation of Bromophycolide F*

Bromophycolides C-I were isolated in 2006, from Fijian Red Algae, *Callophycus serratus*.[50] The bromophycolides are from a group of rare diterpene-benzoate macrolides,

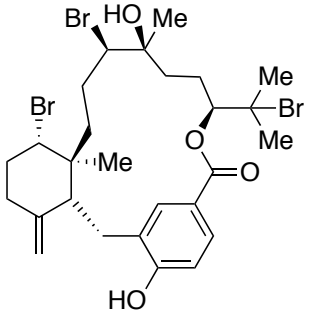
[50] (a)Kubanek, J.; Giese, R. A.; Fairchild, C. R.; Hay, M. E.; *J. Nat. Prod.* **2006**, *69*, 731. (b) Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Fairchild, C. R.; Aalbersberg, W.; Hay,

and at the time of their isolation were found to display moderate levels of antineoplastic activity against a range of different human tumor cell lines. Specifically, bromophycolide F **4.59** had an average $IC_{50}$ of 41.3 $\mu$M across 11 cancer cell lines, and exhibited antifungal activity against amphotericin B-resistant *Candida albicans* ($IC_{50}$ of 240 μM) (Scheme 4.28).[50] To date only the skeletons of bromophycolide A and D have been synthesized by the Krauss laboratory.[51]

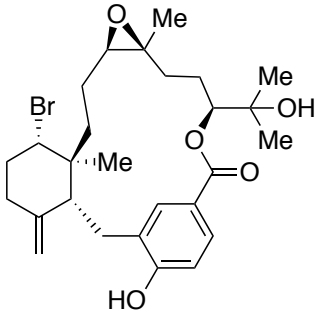
**Scheme 4.28: Selected Members of the Bromophycolide Family**




**4.101**
Bromophycolide A




**4.102**
Bromophycolide D




**4.59**
Bromophycolide F

### *4.4.2. Previous Studies Towards the Synthesis of Bromophycolide A and D*[51]

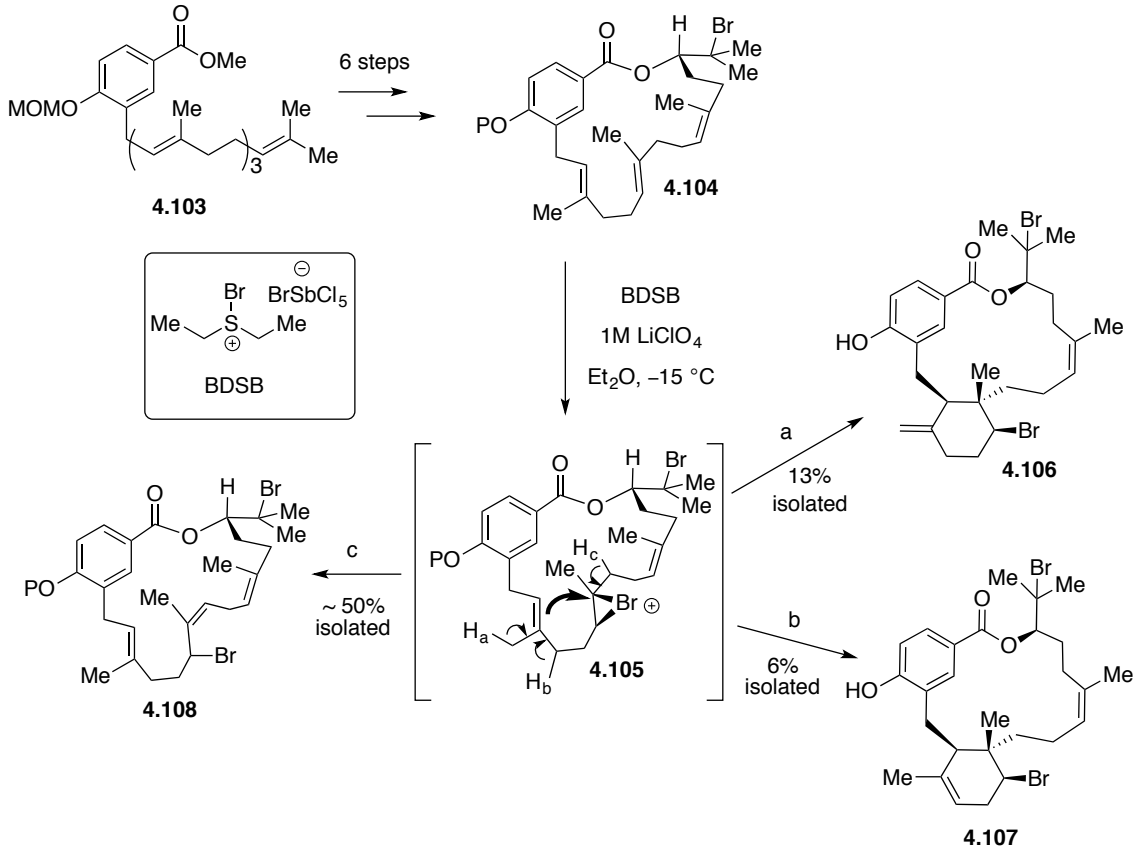
In 2011, the Krauss laboratory presented the asymmetric synthesis of the skeletons of bromophycolide A and D. Their strategy relied on formation of macrocycle

M. E. *J. Nat. Prod.* **2006**, *69*, 73.
[51] Lin, H.; Pochapsky, S. S.; Krauss, I. *J. Org. Lett.* **2011**, *13*, 1222.

**4.104**, and then performing a regio- and diastereoselective bromine-promoted transannular cyclization (Scheme 4.29). The precursor macrocycle **4.104** is available in 6 steps from geranylgeranylated benzoate **4.103**, employing a Sharpless asymmetric dihydroxylation with the specialized Corey-Noe-Lin Ligand to establish the stereochemistry.[52] After extensive screening it was found that Snyder's brominating agent (bromodiethylsulfonium bromopentachloroantimonate, BDSB)[53] , was able to convert macrocycle **4.104** to a mixture of products (Scheme 4.29). The majority of the mixture is elimination product **4.108**. The authors propose that due to the molecule's geometry, attack on the bromonium by the desired alkene is too slow to compete with loss of proton c. Though the majority of the mixture was undesired **4.108**, desired products **4.106** and **4.107** were isolated from the mixture in 13% and 6% yields respectively. This synthesis demonstrates a very interesting transannular cyclization, however, inability to outcompete the elimination pathway limits its utility.

[52] Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741.
[53] (a) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303. (b) Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed*. **2009**, *48*, 7899–7903.

**Scheme 4.29: Krauss Synthesis of Bromophycolide A and D Skeletons**

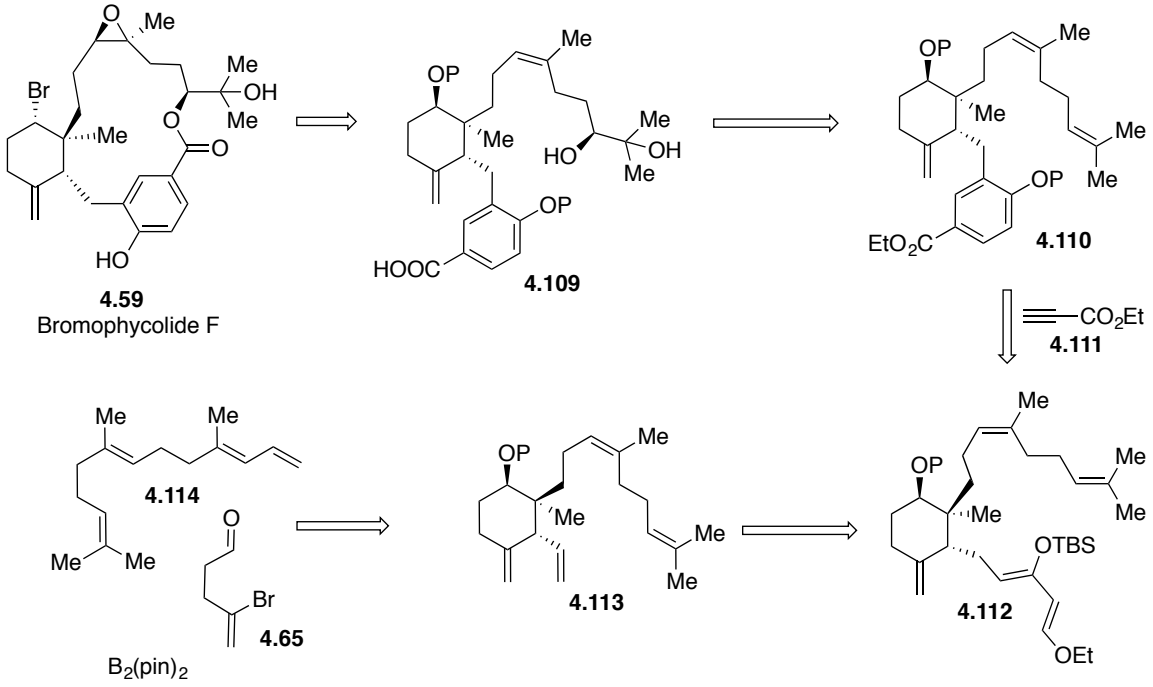



*4.4.3. Retrosynthesis and Model Systems*

We envisioned that our newly developed DACC could provide a more reliable synthetic route to these types of scaffolds. Specifically, DACC with farnesol derived diene **4.114** and aldehyde **4.65** would provide the majority of the carbon skeleton (Scheme 4.30). In order to elaborate the vinyl group to the desired benzoate we considered extending the olefin to a Danishefsky-type diene **4.112** and performing a Diels-Alder reaction with ethyl propiolate. Chemoselective dihydroxylation could be achieved using a Sharpless dihydroxylation, which was also used by the Krauss laboratory.[52] Ideally marcolaconization could then be performed to form the smaller ring with the less

hindered hydroxyl group. One of the major foreseeable challenges is performing an invertive bromination on a hindered secondary alcohol in the last steps of the synthesis. We began our synthetic efforts by investigating these crucial, challenging reactions on model systems.

**Scheme 4.30: Retrosynthesis of Bromopycolide F**



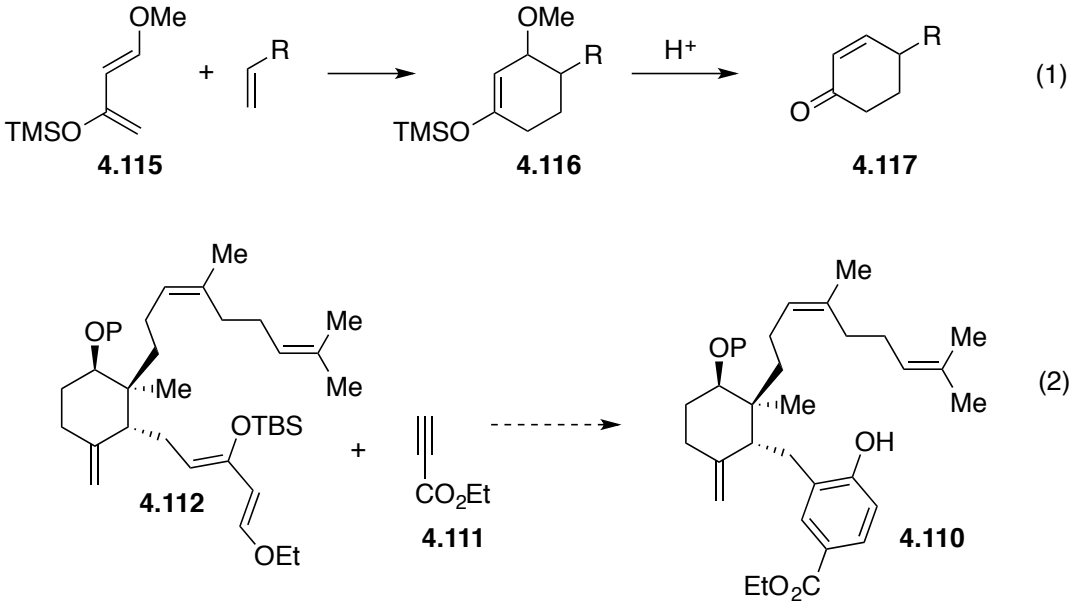

*4.4.3.1. Synthesis of Danishefsky-Type Diene and Model [4+2] Cycloaddition*

Siloxy dienes (such as **4.115**), also known as Danishefsky dienes, have found extensive use in [4+2] cycloaddition reactions.[54] Due to the substitution pattern and electron-richness, these dienes react quickly and regioselectivity in Diels-Alder reactions.

[54](a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. (b) Danishfsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

Importantly, acidic work up yields highly useful cyclohexanone derivatives (Scheme 4.31, eq. 1). The proposed [4+2] cycloaddition in the bromophycolide F synthesis uses an internal siloxy diene[55] (**4.112**) and an alkynyl containing dienophile[56] (**4.111**), both of which have seen limited use in Diels-Alder reaction (Scheme 4.31, eq. 2). In addition, the combination of these partners in an intermolecular Diels-Alder reaction has not been disclosed.[57]

**Scheme 4.31: Examples of Danishefsky's Diene in Diels-Alder Reactions**



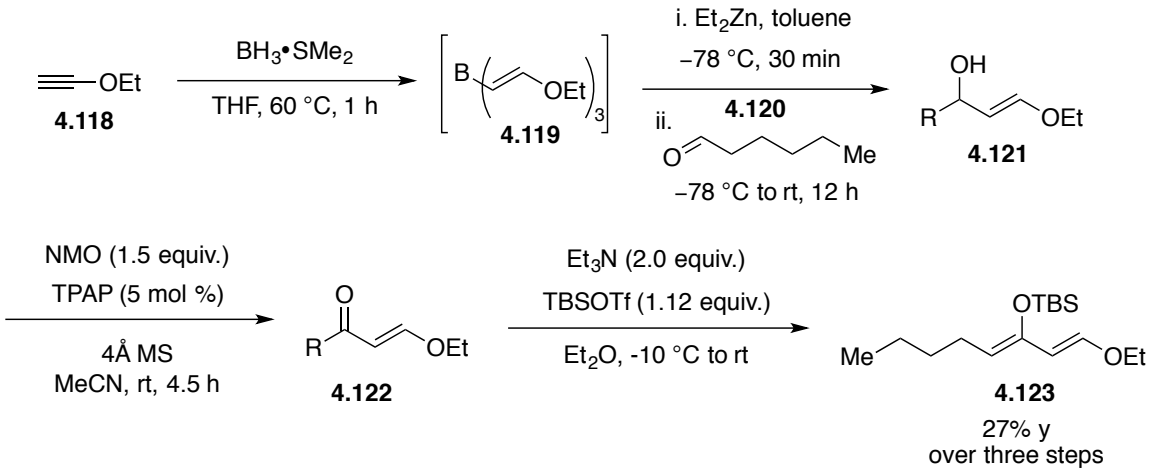

[55] For examples of internal siloxy dienes in Diels-Alder reactions see: (a) Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Angew. Chem. Int. Ed.* **2004**, *43* (b) Yamashita, Y.; Saito, S.; Isitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793. (c) Aben, R. W.; Scheeren, H. W. *Synthesis*, *9*, 779. (d) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082.

[56] For examples of [4+2] reactions with alkynyl dienophiles with Danishefsky dienes see: (a) Pichon, N.; Harrison-Marchand, A.; Toupet, L.; Maddaluno, J. *J. Org. Chen.,* **2006**, *71*, 1892. (b) Sudo, Y.; Shirasaki, D.; Harada, S.; Nishida, A. *J. Am. Chem. Soc,* **2008,** *130,* 12588.

[57] For an example of an intramolecular [4+2] with these partners see: Kusama, H.; Karibe, Y.; Imai, R.; Onizawa, Y.; Yamabe, H.; Iwasawa, N. *Chem.-Eur. J.* **2011**, *17*, 4839.

We decided to investigate the proposed [4+2] cycloaddition with internal siloxy diene **4.123** as a model diene. The model diene was prepared from hexanal, using a two carbon homologation procedure developed by Walsh and co-workers (Scheme 4.32).[58] After formation of the hydroxyl enol ether **4.121**, oxidation followed by silylenol ether formation, gives the desired product in 27% yield over three steps.

**Scheme 4.32: Synthesis of Model Siloxy Diene via Two-Carbon Homologation of Hexanal**

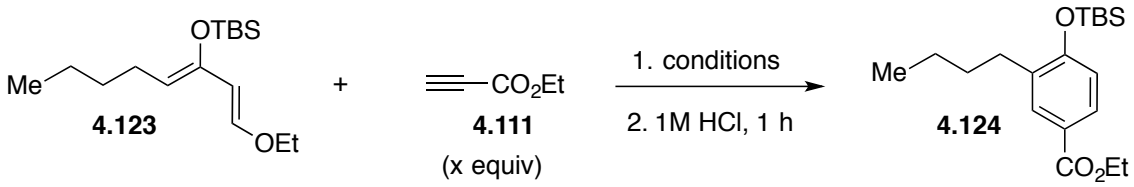



With our model diene in hand, we were pleased to see that refluxing in xylenes with ethyl propiolate **4.111** followed by acidic work up yielded **4.124** as the only regioisomer, albeit in low yield (Table 4.9, entry 1). We proposed that perhaps due to the high temperatures, **4.111** was lost during the reaction due to evaporation or decomposition.[59] Indeed, lowering the temperature and refluxing in toluene resulted in higher yields (entry 2), which could be enhanced by conducting the reaction neat in the

[58] Lurain, A.E.; Carroll, P. J.; Walsh, P. J. *J. Org. Chem.* **2004**, 69, 1262.
[59] The boiling point of ethyl propiolate is 120 °C, boiling point of xylenes is 140 °C, Aldrich

dienophile (entry 3). With evidence that the proposed partners for the Diels-Alder give the desired regiosiomer of product, further optimization would be performed in the desired system.

**Table 4.9: Initial Investigation into [4+2] with Ethyl Propiolate**




| entry | x equiv. | conditions | yield |
|---|---|---|---|
| 1 | 1.5 | xylenes, reflux, 4 days | 10% |
| 2 | 1.5 | toluene, reflux, 3 days | 44% |
| 3 | 6 | neat, reflux, 24 h | 52% |

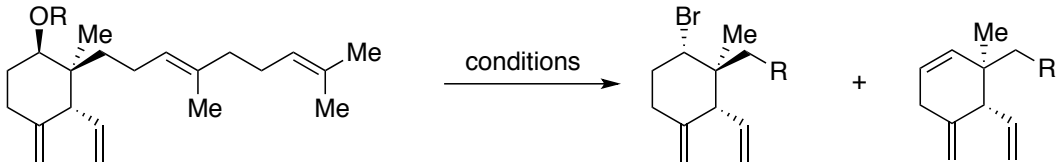
*4.4.3.2. Survey of Potential Bromination Strategies with Model Systems*

Selective bromination of hindered secondary alcohols is often challenging and has been described as such by several authors in their efforts to synthesize brominated natural products.[60] Due to previous difficulties in these reactions we considered that **4.125** could be a model substrate for the bromination, as the steric bulk surrounding the alcohol remains relatively similar throughout the synthesis. We initially looked at direct

[60] (a) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, 117, 5958. (b) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029. (c) Park, J.; Kim, B.; Kim, H.; Kim, S.; Kim, D. Angew. Chem. Int. Ed. **2007**, *46*, 4726.

conversion of the alcohol *via* alkoxyphosphonium intermediates with various bromine sources (Table 4.10, entries 1-4), which resulted in either no conversion of the alcohol or elimination byproduct **4.128**. We also saw elimination as the major product when attempting $S_N2$ displacement of tosylate groups (entry 5, 6).

**Table 4.10: Initial Investigation into $S_N2$-Bromination**




R= H **4.125**
R= Ts **4.126**

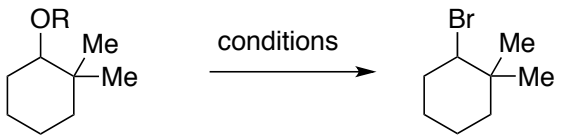
**4.127** **4.128**

| entry | R | reagents | temp. | solvent | results |
|---|---|---|---|---|---|
| 1 | H | $CBr_4$, $PPh_3$, $iPr_2NEt$ | rt | $CH_2Cl_2$ | 50% **4.125** |
| 2 | H | $CBr_4$, $PPh_3$, $iPr_2NEt$ | 40 °C | $CH_2Cl_2$ | 62% **4.128** |
| 3 | H | NBS, $PPh_3$ | rt | $CH_2Cl_2$ | 14% **4.127**, 36% **4.128** |
| 4 | H | $Br_2$, $PPh_3$ | rt | $CH_2Cl_2$ | 20% **4.128** |
| 5 | Ts | $Bu_4NBr$ | rt | DMF | 86% **4.125** |
| 6 | Ts | $Bu_4NBr$ | 40 °C | DMF | 67% **4.128**, 20% **4.125** |

Instead of continuing our investigation on precious intermediate **4.125**, we synthesized simple cyclohexanol derivative **4.129** to look at a broader range of conditions. We were pleased to see that just using boron tribromide or phosphorus tribromide gave the desired product without any trace of elimination byproduct (Table 4.11, entry 1, 2). Thionyl bromide, which was successfully used by Lee and co-workers in the synthesis of

(*3Z*)-Dactomelyne where other bromination strategies failed,[61] was not successful in our system. The highest yields with our model substrate were obtained using an iron(III)-catalyzed halogenation developed by Martin and co-workers.[62]

**Table 4.11: Initial Investigation into $S_N1$-Bromination with Model System**




**4.129** **4.130**

| entry | R | conditions | $^1$H-NMR yield[a] |
|---|---|---|---|
| 1 | H | $BBr_3$ (3 equiv.), $CH_2Cl_2$ | 14% |
| 2 | H | $PBr_3$ (1.1 equiv.), $Et_2O$ | 44% |
| 3 | H | $SOBr_2$, toluene | decomposition |
| 4 | Ms | TMSBr, $Fe(acac)_3$ (10%), $CH_2Cl_2$ | 58% |

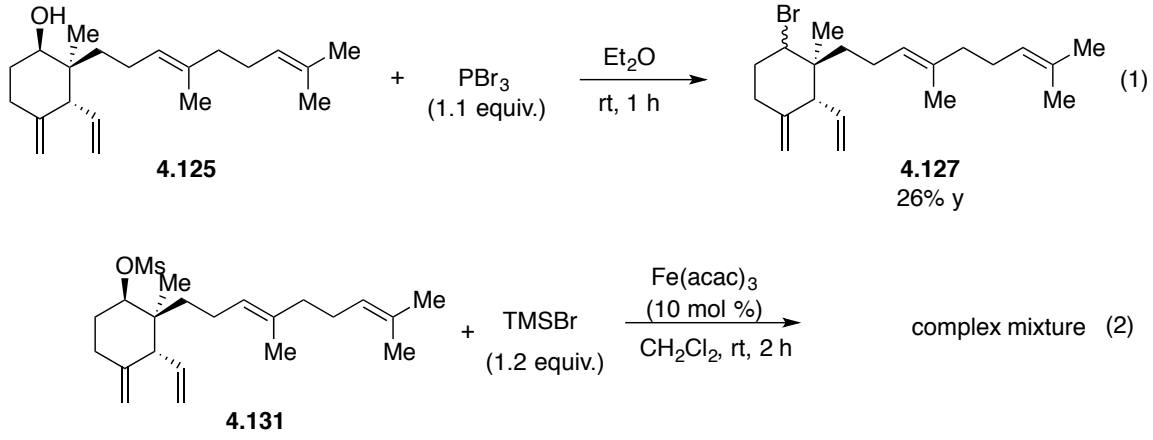
[a] measure by $^1$H-NMR with 1,3,5-trimethoxybenzene as internal standard

In order to further probe the predicted success of these methods in our synthesis, we examined them with our initial model substrate **4.125**. Subjecting the model substrate to bromination with $PBr_3$ in diethyl ether, resulted in a 26% yield of the desired product as a mixture of diastereomers (Scheme 4.33, eq. 1). Though this strategy does give the

[61] Kozikowiski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863.
[62] Ortego, N.; Voelger-Feher, A.; Brovetto, M.; Pardron, J.; Martin, V. S.; Martin, T. *Adv. Synth. Catal.* **2011**, *353*, 963.

desired product, we would prefer a method that can give a stereospecific bromination. Unfortunately, the iron-catalyzed bromination failed with this substrate and gave a complex mixture of products (Scheme 4.33, eq. 2). It seems as though perhaps the best way to investigate the bromination is on the real structure, since the functional groups in the final target are very different from those in **4.125**.

**Scheme 4.33: Optimized Bromination with Original Model System**

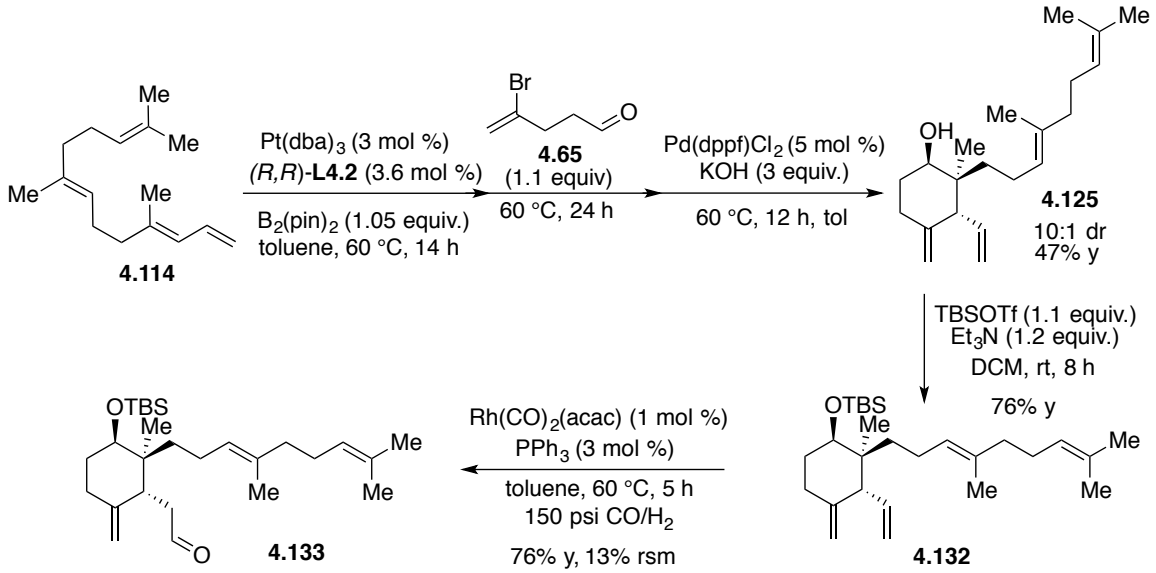



### *4.4.4. Forward Progress*

During the investigation of the model substrates, we began to develop other aspects of the bromophycolide F synthesis. Diboration/allylation/cross-coupling with farnesol-derived diene **4.114** proceeded smoothly to give **4.125** in moderate yield and high diastereoselectivity (Scheme 4.34). It is important to note that the diastereomers can be separated by silica gel column chromatography. In order to elaborate the vinyl chain to the desired siloxy diene, we first needed to perform a linear and chemoselective hydroformylation. After protection of the alcohol we were pleased to see that using

triphenylphosphine as the ligand with a rhodium catalyst gave the desired product **4.133** in 76% isolated yield.

**Scheme 4.34: Forward Progress in Synthesis of Bromophycolide F**



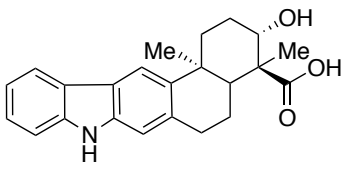

Without a reliable method to install the bromide, we considered that perhaps our synthetic efforts could be put to use with a different target. Though significant work remains to complete the synthesis of bromophycolide F, we have shown that a [4+2] cycloaddition with proparyl dienophiles and internal siloxy dienes proceeds in high regioselectivity and moderate yield. Beyond the bromination there are several remaining challenges: (1) regioselective macrolactonization, (2) implementing the [4+2] cycloaddition in the forward synthesis, and (3) the order in which the epoxidation, dihydroxylation, and bromination are performed.

## 4.5 Progress Towards the Total Synthesis of Xiamycin A

### *4.5.1. Background and Isolation of Xiamycin A*

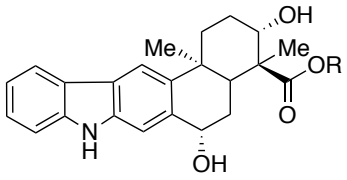
Xiamycin A is a member of the indolosesquiterpenoid family of natural products (4.60, Scheme 4.35). [63] Unlike other members of the inodolosesquiterpenoid family, which are found as metabolites from plants in the Annanacae family,[64] it was isolated from bacteria in 2012. Fairly recently, another group of xiamycins (C-E) were isolated from a different marine bacteria. Xiamycins (C-E) were found to possess biological activity against Porcine epidemic diarrhea virus, [65] and xiamycin A was discovered to be a selective anti-HIV agent.[66] Due to its anti-viral activity xiamycin A has garnered much attention from the synthetic community.

**Scheme 4.35: Xiamycin Derivatives**



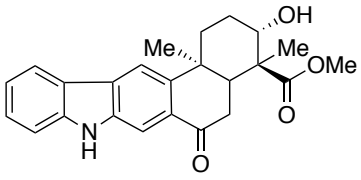

4.#

Xiamycin A




4.#

Xiamycin C: R = H
Xiamycin D: R = Me




4.#

Xiamycin E

[63] Li, H.; Zhang, Q.; Li, S.; Zhu, Y.; Zhang, G.; Zhang, H.; Tian, X.; Zhang, S.; Ju, J.; Zhang, C. *J. Am. Chem. Soc.* **2012**, 134, 8996.

[64] Waterman, P. G. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W.; Ed.; John Wiley & Sons: New York, 1985; vol. 3, chapter 2, pp 99.

[65] Kim, S. H.; Ha, T. K.; Oh, W. K.; Shin, H.; Oh D. C. *J. Nat. Prod.* **2016**, *79*, 51.

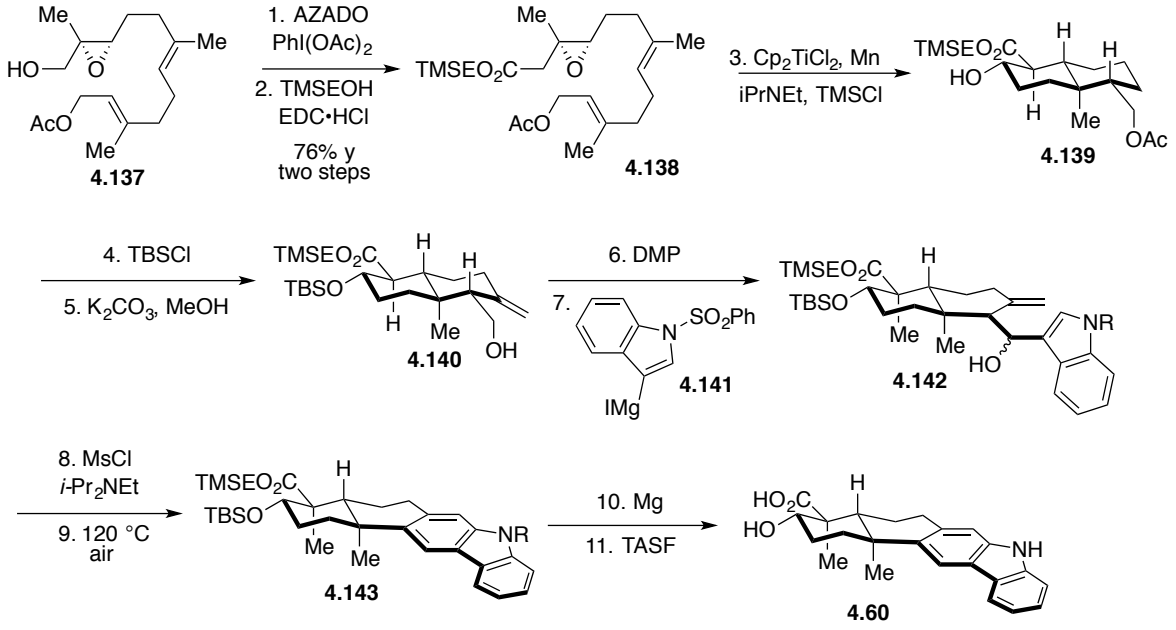
[66] Ding, L.; Munch, J.; Goerls, H.; Maier, A.; Fiebig, H.-H.; Lin, W.-H.; Hertweck, C. *Bioorg. Med. Chem. Lett.* **2010**, *20,* 6685.

*4.5.2. Previous Synthesis of Xiamycin A*

In 2014, Ang Li and co-workers presented syntheses of members of the oridamycin family and xiamycin A.[67] In addition, the group further investigated the biological activity of xiamycin A and found it to be a potent agent against herpes simplex virus-1 *in vitro.* Xiamycin A was synthesized in 11 steps from optically active epoxide **4.137** (Scheme 4.36), in 18.6% overall yield. After oxidation and esterification of **4.137**, a titanium-catalyzed radical epoxypolyene cyclization was used to form the *trans*-decalin **4.139** as a single diastereomer. After a series of protections/deprotections, oxidation of **4.140** followed by Grignard addition leads to the precursor **4.142**. The proposed 6π-electrocyclization/aromatization to form the carbazole proceeded smoothly under microwave irradiation after dehydration of **4.142**. Finally, desulfonylaton of the carbazole followed by deprotection of the acid, yielded xiamycin A **4.60**.

[67] Meng, Z,; Haixin, Y,; Li, L.; Wan, M.; Yang, P.; Edmonds, D. J.l; Zhong, J.; Li, A. *Nature Comm.* **2015**, *6*, 6096.

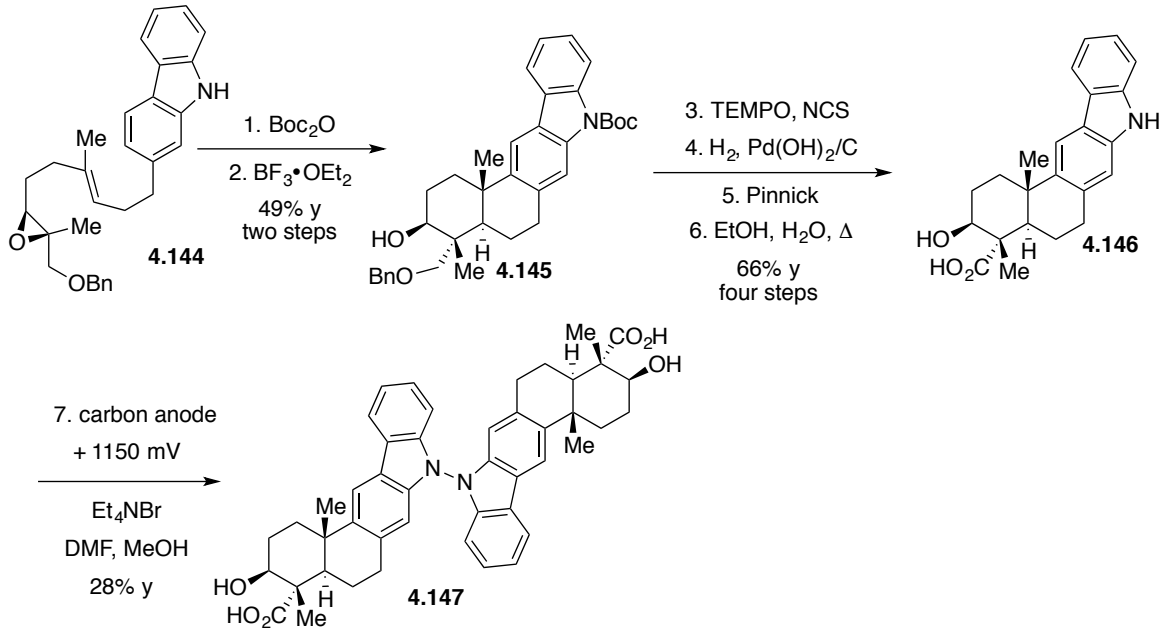
**Scheme 4.36: Synthesis of Xiamycin A by Li and Co-workers**




In 2014, Phil Baran presented the synthesis of dixiamycin B **4.147** through a direct oxidative N-N dimerization of xiamycin A **4.60** (Scheme 4.37).[68] The carbon skeleton of xiamycin A was formed through a cation-olefin cyclization of **4.144**, which is synthesized in 9 steps from geraniol. After cyclization/deprotection of the carbazole, oxidation of the primary alcohol to the acid yields the desired xiamycin A precursor. Dixiamycin B **4.147** was then formed through an electrochemical dimerization, demonstrating the advantages of using this type of strategy to dimerize heterocycles.

[68] Rosen, B. R.; Werner, K. W.; O'Brien, A. G.; Baran, P. S.; *J. Am. Chem. Soc.* **2014**, *136*, 5571.

**Scheme 4.37: Total Synthesis of Dixiamycin B by Electrochemical Dimerization of Xiamycin A**



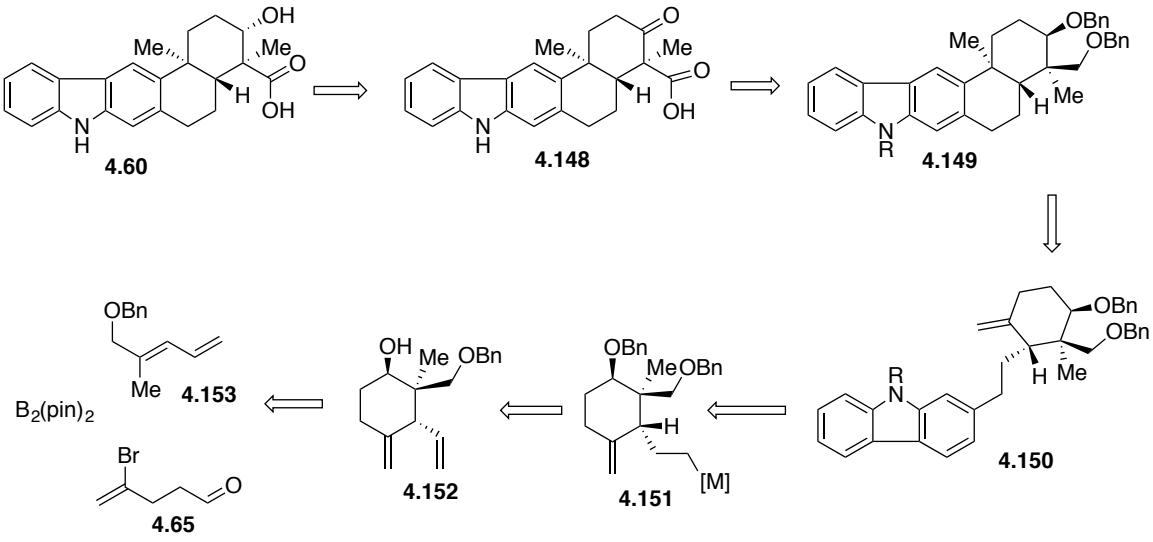

*4.5.3. Retrosynthesis*

Though the previous syntheses of xiamycin A are efficient and high-yielding, we considered that demonstrating a different way of forming the carbocylic core could be useful. We proposed that after asymmetric diboration of diene **4.153**, allylation with **4.65** and cross-coupling would give the cyclohexenol core **4.152**. The carbazole fragment would be appended through a hydrometallation/cross-coupling. The key to the last ring closure would be an intramolecular electrophilic hydroarylation of the exocyclic alkene **4.150**.[69] Deprotection of the alcohols followed by oxidation would

[69] (a) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581. (b) Cacciuttolo, B.; Poulain-Martini, S.; Dunach, E. *Eur. J. Org. Chem*. **2011**, 3710. (c) Jean, M.; van de Weghe, P. *Tetrahedron Lett.* **2011**, *52*, 3509 (d) Shigehise, H.; Ano, T.; Honma, H.;

give ketoacid **4.148**, and substrate controlled reduction would yield the desired product.[70]

**Scheme 4.38: Retrosynthesis of Xiamycin A using DACC**




*4.5.4. Forward Progress*

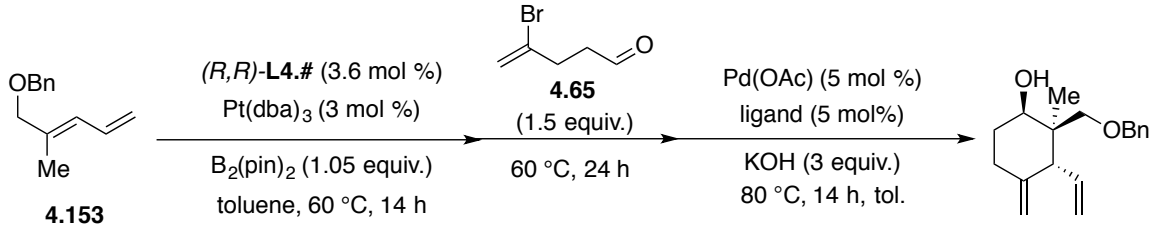
The first key step of our synthesis is the hydrometallation/cross-coupling to append the carbazole, as we predicted that a hydroboration followed by a Suzuki cross-coupling would be a feasible strategy. In order to test this, we needed to first perform the diboration/allylation/cross-coupling with diene **4.153**. Unfortunately,

Ebisawa, K.; Hiroya, K. *Org. Lett.* **2016**, *18*, 3622. (e) Crossley, S. W. M.; Martinez, R. M.; Guevara-Zuluaga, S.; Shenvi, R. A. *Org. Lett*. **2016**, *18*, 2620.

[70] Li, H.; Zhang, Q.; Li, S.; Zhu, Y.; Zhang, G.; Zhang, H.; Tian, X.; Zhang, S.; Ju, J.; Zhang, C. *J. Am. Chem. Soc.* **2012**, 134, 8996.

with this diene the DACC gave lower diastereoselectivity than the corresponding geraniol derived diene **4.31**. To see if the selectivity could be further improved we surveyed a small set of ligands (Table 4.12). However, it seemed that dppf still gave the highest yield and diastereoeselectivty, and the synthesis was continued using these conditions.

**Table 4.12: Screening Ligands for DACC with Diene 4.153**




| entry | ligand | yield | dr |
|---|---|---|---|
| 1 | $PCy_3$ | < 5% | -- |
| 2 | $P(t\text{-}Bu)_3$ | < 5% | -- |
| 3 | dppf | 46% | 4:1 |
| 4 | *rac*-BINAP | < 5% | -- |
| 5 | RuPhos | 19% | 2.6:1 |

[a] diastereomer ratios were determined by $^1$H-NMR

With **4.152** in hand, we proposed to employ a hydroboration with 9-BBN followed by a cross-coupling with unprotected 2-bromo[9H]carbazole **4.155**. Compared to their B(pin) analogs, ross-couplings of alkyl 9-BBN compounds can be performed at lower temperatures with weaker bases, due to the ease of transmetalation of boranes compared to the corresponding boronic esters.[71] We were pleased to see that using

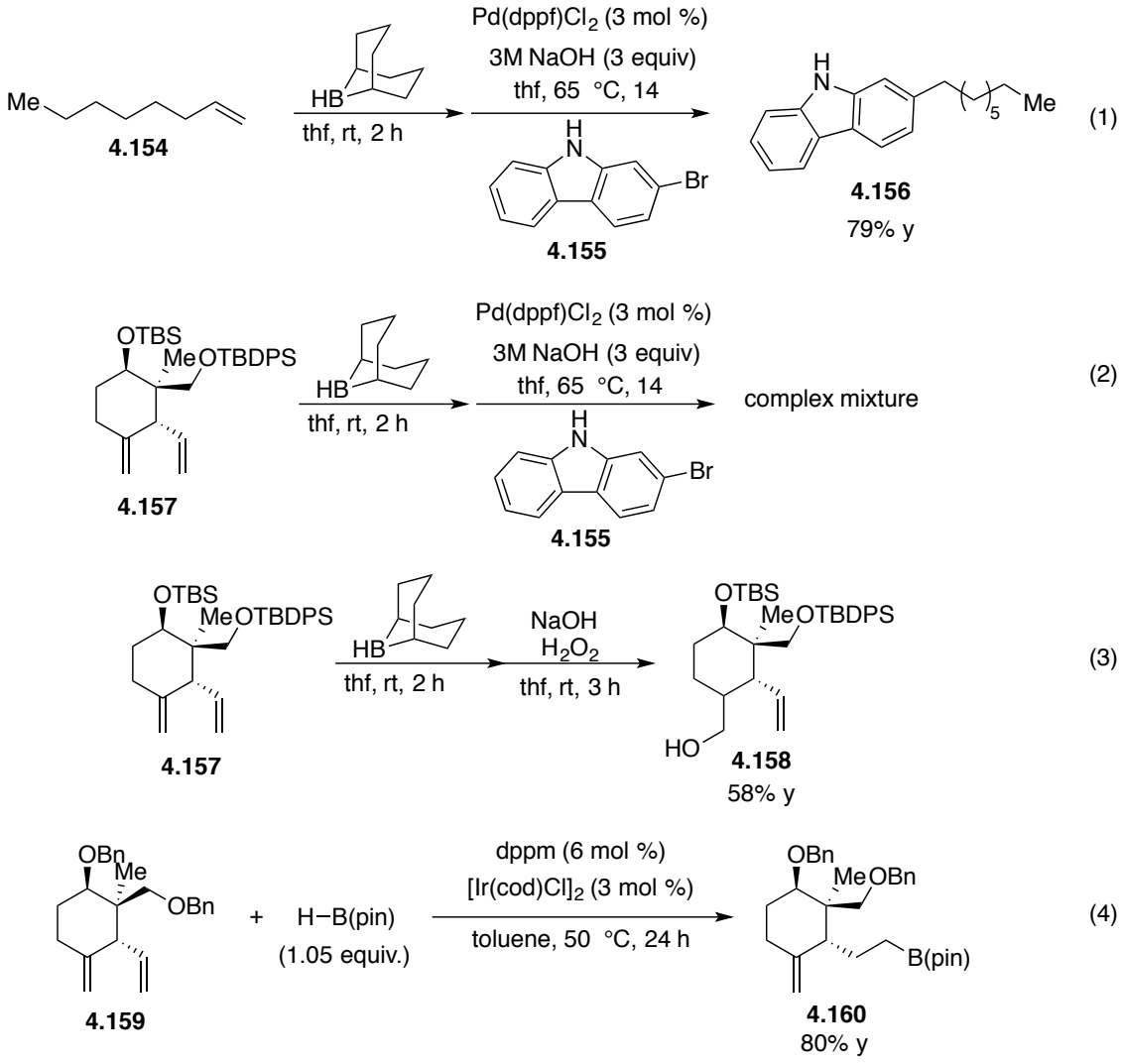
[71] Lennox, J. J. A.; Lloyd-Jones, G. C. *Chem. Soc. Rev.*, **2014**, *43*, 412.

conditions developed by Vice *et al.*, hydroboration and cross-coupling on 1-octene as a model system resulted in the desired cross-coupled product in high yield (Scheme 4.39, eq. 1).[72] However, application of these conditions to our synthetic intermediate **4.157**, lead to a complex mixture of products (eq. 2). This is not that surprising since H. C. Brown has shown that hydroboration of 1,1-disubstituted alkenes occurs at a faster rate than with monosubsituted olefins.[73] Indeed, performing a 9-BBN hydroboration followed by oxidation of **4.157** revealed alcohol **4.158** as the only regioisomer (eq. 3).

[72] (a) Vice, S.; Bara, T.; Bauer, A.; Evans, C. A.; Ford, J.; Josien, H.; McCombie, S.; Miller, M.; Nazareno, D.; Palani, A.; Tagat, J. *J. Org. Chem.* **2001**, *66,* 2487. For a review of B-Alkyl Suzuki-Miyaura Cross-Couplings see; Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.,* **2001**, *40*, 4544.

[73] Brown, H. C.; Ramachandran, P. V.; Prassad, J. V. N. V. *J. Org. Chem.,* **1985**, *50*, 5583.

**Scheme 4.39: Investigation of Hydroboration Cross-Coupling with 9-BBN in THF**

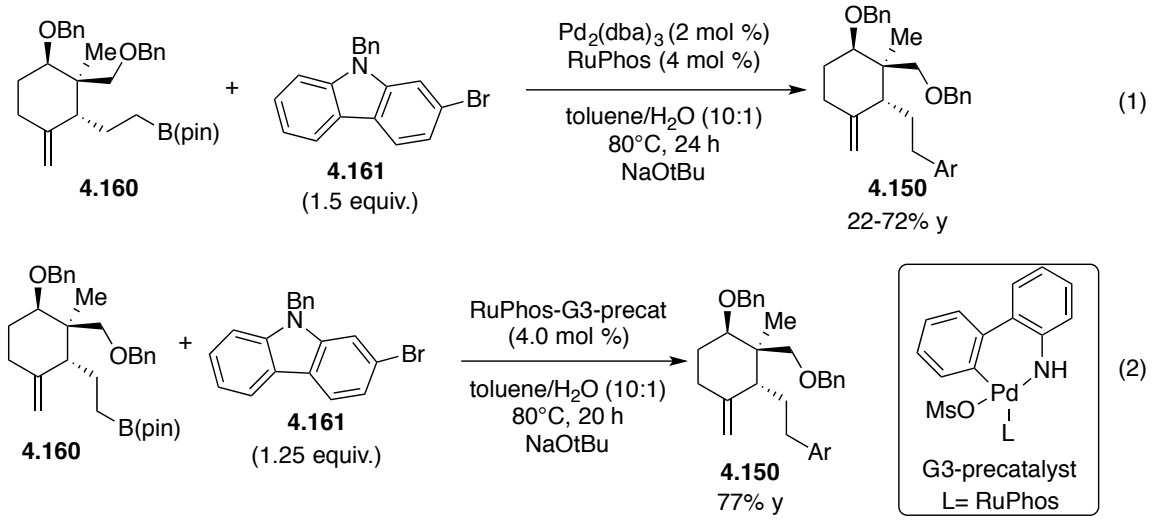



Due to the rate difference in hydroboration between the two olefins with 9-BBN, it seemed as though a new hydroboration strategy would be necessary. Rh- and Ir-cataylzed hydroboration with catecholborane and pinacolborane has been demonstrated to be selective for terminal olefins over 1,1-disubsituted olefins.[74] We were pleased to see that Ir-catalyzed hydroboration of **4.159** with pinacol borane yielded the desired

[74] Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671.

products in high yield as the only regioisomer (Scheme 4.40, eq. 4).[75] After purification of alkylboronic ester **4.160**, we were able to perform the desired cross-coupling with Bn-protected carbazole **4.161** using conditions developed by Marder and co-workers (Scheme 4.41, eq. 1).[76] However, under these conditions it was difficult to obtain reproducible yields. We considered that variability could be due to inconsistency between different batches of $Pd_2(dba)_3$. It has been shown that different commercial sources of this palladium precatalyst have purities ranging from 64 -92%.[77] Employing a Buchwald third-generation RuPhos precatalyst leads to a more reliable cross-coupling.[78]

**Scheme 4.40: Condition Screening for Cross-Coupling of Alkylboronic Ester with Carbazole 4.161**

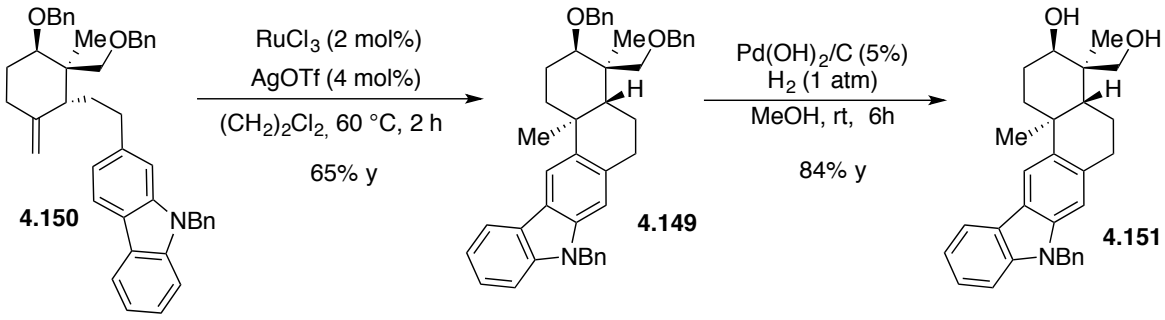



In order to complete the synthesis, the next step is an intramolecular hydroarylation. Applying conditions by Sames and co-workers,[69a] **4.150** was treated

[75] Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron* **2004**, *60*, 10695.
[76] Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem. Int. Ed.,* **2012**, *51***,** 528.
[77] Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302.
[78] Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 2876.

with catalytic ruthenium(III) chloride and AgOTf at 60 °C this gave the desired cycle in moderate yields (Scheme 4.41).

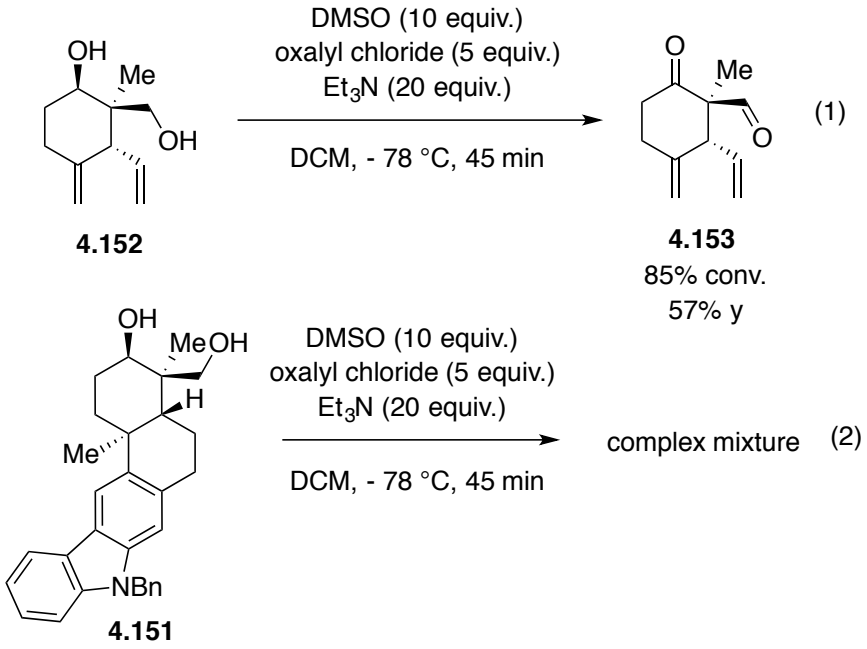
**Scheme 4.41: Intramolecular Electrophilic Arylation and Deprotection to Access Xiamycin A Scaffold**




Although we were able to build the carbon scaffold of xiamycin A, oxidation of diol **4.151** failed to give the desired keto-aldehyde and lead to a complex mixture of inseparable products.[79] This was surprising because we had previously investigated this oxidation on model substrate **4.152**, where the desired product was formed exclusively (Scheme 4.42). In order to solve this issue, two different protecting groups should be employed to allow for selective deprotection and oxidation of the different alcohols. This was never attempted; with the extra steps added to the synthesis our proposed route to xiamycin A would be longer and lower yielding than the syntheses presented by Ang Li and Phil Baran. The diboration/allylation/cross-coupling turned out to not be a better strategy for the synthesis of this particular natural product, but we were able to demonstrate that the carbon framework could be built-up with the strategy presented.

[79] This was the outcome with other oxidants as well: DMP, TPAP/NMO, IBX.

**Scheme 4.42: Investigation into Oxidation of Diol to Ketoaldehyde.**




## 4.6 Conclusions

To summarize, we have optimized the reaction conditions for the intramolecular allyl-aryl cross-coupling step of a sequential asymmetric diboration/allylation/cross-coupling to access carbocycles. We have shown that two different sets of conditions are need for the cross-coupling depending on the ring size. To furnish enantioenriched cyclohexenols use of $Pd(dppf)Cl_2$ with KOH base gives the highest yields and diastereselectivities. To furnish enantioenriched cyclobutenol and cyclopentenol cores use of $Pd(OAc)_2$, XPhos and CsF as the base gives the higheset yields and diastereoselectivities. Furthermore, we have shown that this method can be applied to the synthesis of the carbon skeleton of xiamycin A. Also, we have shown that this method

could be employed in the total synthesis with bromophycolide F, when an efficient bromination is found.

## 4.7 Experimental

### 4.7.1 General Information

$^{1}$H-NMR spectra were recorded on a Varian Gemini-500 (500 MHz), Varian Inova 500 (500 MHz) or Varian Gemini-600 (600 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as the following: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent), and coupling constants (Hz). Coupling constants are reported to the nearest 0.5 Hz. 13C NMR spectra were recorded on a Varian Gemini-500 (125 MHz) or Varian Gemini-600 (151 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.0 ppm). Infrared (IR) spectra were recorded on a Burker alpha spectrophotometer, $\nu_{max}$ $cm^{-1}$. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High-resolution mass spectrometry (DART-TOF) was performed at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel ($SiO_2$, 230×450 Mesh) purchased from Silicycle. Automated column chromatography was performed using silica gel cartridges on a Biotage Isolera Single

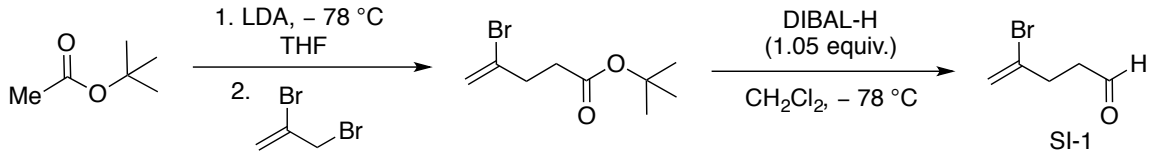
Channel System with variable detector. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate ($KMnO_4$) in water, or phosphomolybdic acid (PMA) in ethanol. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. Analytical chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon, unless otherwise stated. Tetrahydrofuran (THF), toluene, diethyl ether ($Et_2O$) and dichloromethane (DCM) were purified using a Pure Solv MD-4 solvent purification system from Inert (previously; Innovative Technology Inc.) by passing through two activated alumina columns after being purged with argon. Bis(pinacolato)diboron was obtained from Frontier Scientific and recrystallized from hot pentane prior to use. (*Z*)-penta-1,3-diene was purchased from TCI. (*Z)*-2-bromo-3-phenylacrylaldehyde was purchased from Aldrich. 2,3-dibromopropene was purchased from AK scientific. Potassium hydroxide was purchased from Fisher Scientific. Cesium fluoride was purchased from Acros. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane palladium (II) acetate, XPhos and tri-*tert*-butylphopshine (10% in hexanes) were purchased from Strem Chemicals. Tris(dibenzylideneacetone)platinum and (*R,R*)-3,5-di-

iso-propylphenylTADDOLPPh were prepared according to the literature procedure.[80] ((6-bromobenzo[*d*][1,3]dioxol-5-yl)methyl)trimethylsilane was prepared according to the literature procedure.[81] All other chemicals were purchased from Aldrich, Fisher Scientific, or Alfa Aesar and used without further purification.

### 4.7.2 Preparation of Electrophiles

*Preparation of 4-bromopent-4-enal*



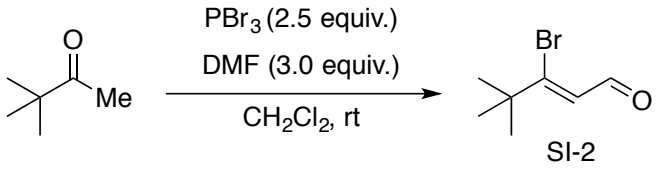

The title compound was prepared according to the literature procedure with slight modification. To a solution of diisopropylamine (3.95 mL, 28.25 mmol) in anhydrous THF (35 mL) at 0 °C was added *n*-BuLi (10.5 mL, 26.25 mmol, 2.5 M in hexanes) dropwise by syringe. The solution was allowed to stir at 0 °C or 1 h under $N_2$. In a separate flask equipped with an addition funnel, a solution of *tert*-butylacetate (3.35 mL, 25.0 mmol) in THF (25 mL) was cooled to -78 °C under $N_2$. The LDA solution was transferred *via* cannula to the addition funnel and added dropwise to the reaction mixture. After stirring at -78

[80] Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. *Nature* **2014**, *505*, 386.
[81] Beard, A. R; Hazell, S. J.; Mann, J.; Palmer, C. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1235.

°C for 1 h, 2,3-dibromopropene (3.05 mL, 25.0 mmol) was added dropwise. The solution was stirred at -78 °C for 2 h before warming to room temperature and allowing to stir for an additional 14 h. After, solvent removed under reduced pressure followed by the addition of $H_2O$ (100 mL). The mixture was extracted with EtOAc (3 x 75 mL), organic layers combined and washed with brine (50 mL) and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude residue was purified by column chromatography (10:1 $Et_2O$:EtOAc) to afford the intermediate ester as an orange oil (5.26 g, 90% y). To a solution of ester in $CH_2Cl_2$ (175 mL) under $N_2$ at $-78$ °C was cannula transferred DIBAL-H (23.6 mmol, 23.6 mL, 1.0 M in $CH_2Cl_2$). Solution allowed to stir at $-78$ °C for 40 min before quenching by the addition of Rochelle's salts (30 mL), solution allowed to warm to room temperature and stir for 14 h. Solution transferred to separatory funnel and organic layer removed, aqueous layer extracted $CH_2Cl_2$ (2 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (10:1 hexanes: EtOAc) to provide the desired product as a light yellow oil (2.17 g, 60% y). All spectral data in accordance with the literature.[82]

*Preparation of (Z)-3-bromo-4,4-dimethylpent-2-enal*

[82] Harris, D. G.; Herr, Jason, R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 5452.

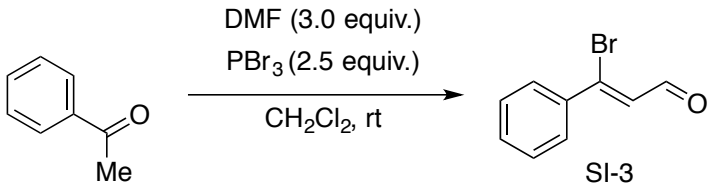



SI-2

The title compound was prepared according to a literature procedure with slight modification.[83] Phosphore tribromide (4.70 mL, 50 mmol) was added dropwise to a solution of DMF (4.67 mL, 60 mmol) in dry $CH_2Cl_2$ (15 mL) at 0 °C. The reaction mixture was stirred at 0°C, until the mixture turned yellow, followed by the dropwise addition of a solution of pinacolone (2.50 mL, 20 mmol) in $CH_2Cl_2$ (10 mL). The reaction was then allowed to warm to room temperature and stir for 14 h. The solution is then cooled to 0 °C and the pH adjusted to 7-8 by addition of aqueous $NaHCO_3$. The mixture is extracted with ethyl acetate and the combined organic phases are washed with water (3 × 20 mL) and brine (1 × 25 mL), dried over sodium sulfate and concentrated to an oil. Purified by automated silica gel chromatography (100g column, 5 to 10% EtOAc in Hexanes) to yield the title compound as a colorless oil (2.16 g, 56% y). IR (neat, $cm^{-1}$): 2972 (m), 2938 (w), 2870 (w), 1681 (s), 1605 (m), 1364 (w), 1124 (m). $^1H$ NMR (600 MHz, $CDCl_3$): $\delta$ 9.93 (s, 1H), 6.35 (s, 1H), 1.28 (s, 9H). $^{13}C$ NMR (151 MHz, $CDCl_3$): $\delta$ 195.1, 162.0, 125.3, 41.1, 29.0. HRMS: (DART) calculated for $C_7H_{12}BrO$ ($[M+H]^+$): 191.0072, found: 191.0061

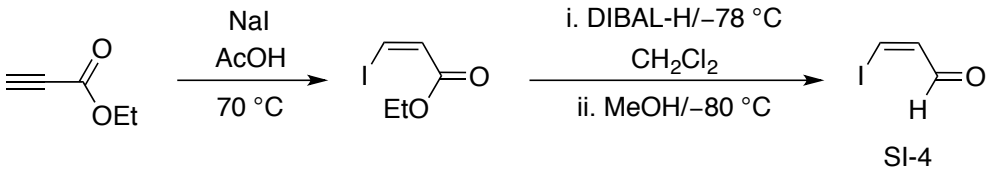
*Preparation of (Z)-3-bromo-3-phenylacrylaldehyde*

[83] Salem, B.; Delort, E.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5*, 2307.




The title compound was prepared according to the same procedure as (Z)-3-bromo-4,4-dimethylpent-2-enal with minor modifications (use of acetophenone instead of pinacolone). The crude product was purified by automated silica gel chromatography (100 g column, 5 to 45% EtOAc in hexanes) to afford the title compound as a yellow oil (648 mg, 30% y). Spectral data are in agreement with the literature.[84]

*Preparation of (Z)-3-iodoacrylaldehyde*



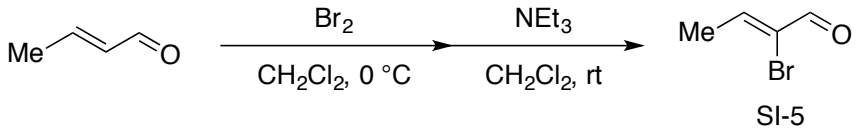

The title compound was prepared according to the literature procedure.[85] To a flame dried round-bottom flask with magnetic stir bar was charged with sodium iodide (10.2 g, 68 mmol) and glacial acetic acid (33.0 mL). To the stirred solution was added ethyl

[84] Zou, X.; Yang, L.; Liu, X.; Sun, H.; Lu, H. *Adv. Synth. Catal.* **2015**, *357*, 3040.
[85] Marek, I.; Meyer, C.; Normant, J.-F. *Org. Synth.* **1997**, *74*, 194.

propiolate (6.9 mL, 68 mmol) and the mixture was then heated in an oil bath at 70 °C for 14 h. The solution was then cooled to room temperature and water (20 mL) and diethyl ether (20 mL) were added. The organic layer was sepearated and extracted with diethyl ether (2 x 5 mL). The combined organic layers were then washed with aqueous 3 M KOH, until the aqueous phase is neutral pH, then washed with brine, and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure and the resulting brown oil was distilled, (Z)-beta-iodoacrylate was obtained as a yellow oil (14.8 g, 93% y). To a solution of iodoacrylate (1.13 g, 5.0 mmol) in dichloromethane (15.0 mL) at $-78$ °C, under $N_2$ was added DIBAL-H (0.90 mL, 5.0 mmol) dropwise such that the internal temperature does not exceed $-75$ °C. The reaction was stirred at $-78$ °C for 30 min, before methanol (2.5 mL) added dropwise followed by the addition of potassium sodium tartrate (12 mL, 20%, aq) in one portion, and cold bath removed. Diethyl ether added to solution and then stirred at room temperature for 20 minutes. The solution was then passed through celite, filtrate was transferred to seperatory funnel and aqeous layer washed with diethyl ether (2 x 10 mL). Organic layers were combined, washed with saturated sodium chloride, dried and filtered. Material concentrated under reduced pressure at 0 °C (product volatile) to yield the desired product as a colorless oil (802 mg, 82% y). Product was stored as a 1.0 M solution in dichloromethane at $-20$ °C. Spectral data is in accordance with the literature.[86]

*Preparation of (Z)-2-bromobut-2-enal*

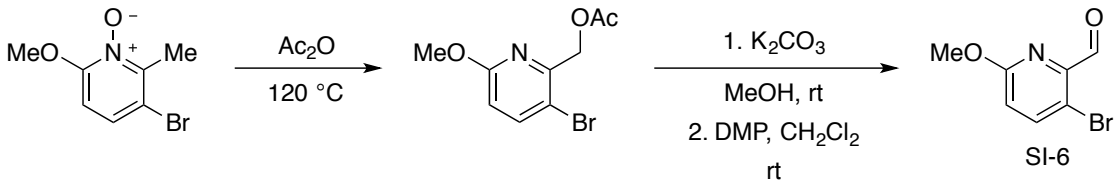
[86] Paterson, I.; Paquet, T.; *Org. Lett*. **2010**, *12*, 2158.




SI-5

The title compound was prepared according to the literature procedure.[84] To a solution of trans-crotonaldehyde (3.0 mL, 36.6 mmol) in dichloromethane (50.0 mL) at 0 °C, was added a solution of bromine (1.9 mL, 37.0 mmol) in dichloromethane dropwise over 10 min. Solution was allowed to stir at 0 °C for 1 h before trimethylamine (6.2 mL, 44.3 mmol) added and reaction warmed to room temperature and stirred for an additional 1.5 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL), and the organic layer was washed with 1 M HCl (10 mL), brine (10 mL), dried filtered, and concentrated under reduced pressure. The desired product was isolated as a pale yellow liquid (5.28 g, 98% y) and used without further purification. Spectral data is in accordance with the literature.[84]

*Preparation of 3-bromo-6-methoxypicolinaldehyde*




SI-6

The title compound was prepared according to the literature procedure.[87] 3-bromo-6-methoxy-2-methylpyridine 1-oxide (1.29 g, 5.9 mmol) was dissolved in acetic anhydride (0.56 mL, 5.9 mmol) and heated to 120 °C for 3 h under nitrogen. Reaction cooled to room temperature, methanol added and solvent removed on a rotary evaporator. The crude produce was dissolved in diethyl ether and then washed with the following; saturated sodium bicarbonate (3 x 5 mL), water (5 mL), and brine (5 mL). The organic layer was then dried over anhydrous sodium sulfate and concentrated by rotary evaporator to yield the crude acetate. To a solution of crued acetate (1.54 g, 5.9 mmol) in methanol (20 mL) was added 1.0 M potassium carbonate (10 mL, 10.0 mmol), the resulting solution was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (15.0 mL) and DMP added and allowed to stir at room temperature until complete by TLC. The reaction was quenched with saturated sodium bicarbonate and then extracted with DCM (2 x 5 mL) dried over anhydrous sodium sulfate and the solvent removed. Reaction mixture was purified by automated column chromatography (50g column, 3 to 30% EtOAc in hexanes). The title compound was obtained as an off white solid (565 mg, 44% y).

### 4.7.3 General Procedure for Diboration/allylation/cross-coupling

*Cross-Coupling Procedure A:*

[87] Kelly, S. A.; Foricher, Y.; Mann, J.; Bentley, J. M. *Org. Biomol. Chem.* **2003**, *1*, 2865.

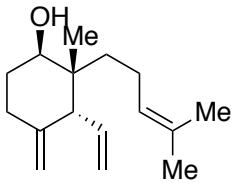
To an oven-dried two-dram vial with magnetic stir bar in the dry box was added $Pt(dba)_3$ (13.5 mg, 0.015 mmol), **L4.2** 16.4 mg, 0.018 mmol), $B_2(pin)_2$ (140 mg, 0.55 mmol) and toluene (0.5 mL, [substrate] = 1.0 M). The vial was sealed with a teflon septum cap, removed from the dry box, and heated to 80 °C in an oil bath for 20 minutes. The vial was cooled to room temperature, returned to the dry box and charged with diene (0.50 mmol). The vial was sealed, removed from the dry box and stirred at 60 °C for 6 h, at which point aldehyde added (0.55 mmol) and stirred for an additional 14 h at 60 °C. The solution was cooled to room temperature and concentrated by rotary evaporation, the placed on high vacuum for 6 to 12 h. After drying the vial containing crude intermediate was purged with $N_2$, returned to the dry box and charged with toluene (2.5 mL), $Pd(dppf)Cl_2$ (20.4 mg, 0.025 mmol) and KOH (84 mg, 1.5 mmol). The vial was sealed with a teflon septum cap, removed from the dry box, and heated at 80 ºC for 14 h. The crude reaction mixture was filtered through a short pad of silica gel and washed with ethyl acetate.

*Cross-Coupling Procedure B:*

To an oven-dried two-dram vial with magnetic stir bar in the dry box was added Pt(dba)3 (13.5 mg, 0.015 mmol), **L4.2** 16.4 mg, 0.018 mmol), $B_2(pin)_2$ (140mg, 0.55 mmol) and toluene (0.5 mL, [substrate] = 1.0 M). The vial was sealed with a teflon septum cap, removed from the dry box, and heated to 80 °C in an oil bath for 20 minutes. The vial was cooled to room temperature, returned to the dry box and charged with diene (0.50 mmol). The vial was sealed, removed from the dry box and stirred at 60 °C for 6 h, at

which point aldehyde added (0.50 mmol) and stirred for an additional 14 h at 60 °C. The solution was cooled to room temperature and concentrated by rotary evaporation, the placed on high vacuum for 1 to 6 h. After drying the vial containing crude intermediate was purged with $N_2$, returned to the dry and charged with tetrahydrofuran (2.5 mL), allowed to stir for 2 min or until homogenous. Then $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), XPhos (11.9 mg, 0.025 mmol), and CsF (228 mg, 1.5 mmol) added sequentially. The vial was sealed with a teflon septum cap, removed from the dry box, and heated at 65 °C in an oil bath at maximum stir rate for 16 h. NOTE: the reaction forms an intractable gum easily, and should be shaken periodically shortly after setup in order to dislodge clumps and maintain. At which point the vial was cooled to room temperature, diluted with water and EtOAc. The organic layer was separated and aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic layers were dried with $Na_2SO_4$, filtered, and concentrated on a rotary evaporator.

### 4.7.4 Compound Characterization and Stereochemical Assignments

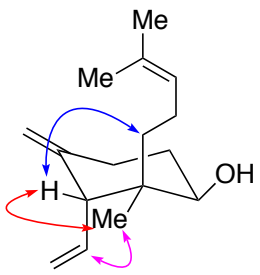


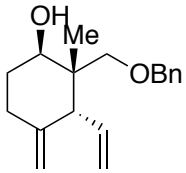

**(1*R*,2*R*,3*R*)-2-methyl-4-methylene-2-(4-methylpent-3-en-1-yl)-3-vinylcyclohexan-1-ol.** Synthesized according to the general procedure A with (*E*)-4,8-dimethylnona-1,3,7-triene (75 mg, 0.50 mmol) and 4-bromopent-4-enal **SI-1** (81 mg, 0.55 mmol. Reaction mixture was purified first by silica gel

chromatography (0 to 10% EtOAc in hexanes). A second silica gel chromatography was performed (100% DCM) to yield the title compound as a single diastereomer, light yellow oil (**Run 1**: 54 mg, 46% yield, 10:1 d.r. **Run 2**: 59 mg, 50% y, 9.8:1 d.r.). $R_f$ = 0.76 in 4:1 Hex:EtOAc, stain in PMA). $[\alpha]^{21}_{D}$ = – 19.98 (c = 1.00 in $CHCl_3$). IR (neat, $cm^{-1}$): 3429 (br), 3075 (w), 2965 (w), 2931 (m), 2875 (m), 1444 (m), 1377 (m), 1123 (s), 838 (s), 1028(w), 971 (s), 447(w).$^1$H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 5.87 (1H, ddd, *J* = 17.1 Hz, 9.8 Hz, 9.8 Hz), 5.14 – 5.00 (2H, m), 5.05 (1H, dd, *J* = 1.5 Hz, 2.9 Hz) 4.80 (1H, s), 4.61 (1H, s), 3.74 (1H, t, *J* = 2.9 Hz), 2.90 (1H, d, *J* = 9.5 Hz), 2.42-2.36 (1H, m), 2.23 – 2.18 (1H, m), 2.02 – 1.88 (2H, m), 1.82 – 1.73 (1H, m), 1.68 (3H, s), 1.61 (3H, s), 1.48 – 1.42 (2H, m), 1.33 – 1.22 (2H, m), 0.86 (3H, s). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 149.0, 136.6, 131.4, 125.0, 117.4, 109.1, 72.2, 53.6, 41.2, 36.1, 30.0, 29.9, 25.7, 21.8, 19.1 17.6 HRMS: (DART) calculated for $C_{16}H_{25}$ ($[M+H–H_2O]^+$): 217.1956, found: 217.1955

***Analysis of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry of the cross-coupling was determined by NOESY analysis. The following NOEs were observed:



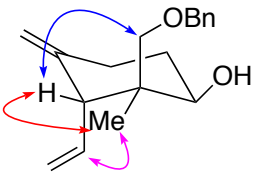


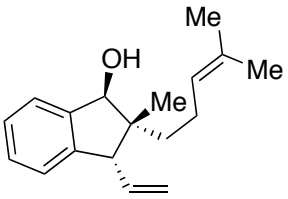

**(1*R*,2*S*,3*R*)-2-((benzyloxy)methyl)-2-methyl-4-methylene-3-vinylcyclohexan-1-ol.** Synthesized according to the general procedure A with (*E*)-(((2-methylpenta-2,4-dien-1-yl)oxy)methyl)benzene (94 mg, 0.50 mmol) and 4-bromopent-4-enal **SI-1** (81 mg, 0.55 mmol). Reaction mixture was purified first by silica gel chromatography (0 to 10% EtOAc in hexanes). A second silica gel chromatography was performed (100% DCM) to yield the title compound as a single diastereomer, light yellow oil (**Run 1**: 57 mg, 42% yield, 4.0:1 d.r. **Run 2**: 70 mg, 52% y, 4.0:1 d.r.). $R_f$ = 0.24 in 10:1 Hex:EtOAc, stain in PMA). $[\alpha]^{21}_D$ = −22.267 (c = 0.455 in $CHCl_3$).IR (neat, $cm^{-1}$): 3480 (br, w), 3074 (w), 3029 (w), 2934 (m), 2860 (m), 1641 (w), 1027 (s), 1004 (s), 918 (m), 890 (m), 609 (m). $^1$H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.31 (m, 5H), 5.85 (dt, *J* = 16.6, 10.2 Hz, 1H), 5.16 – 5.13 (m, 2H), 4.82 (s, 1H), 4.59 (s, 1H), 4.47 (s, 2H), 4.19 (s, 1H), 3.80 (s, 1H), 3.54 (d, *J* = 9.2 Hz, 1H), 3.35 (d, *J* = 9.2 Hz, 1H), 3.31 (d, *J* = 9.8 Hz, 1H), 2.54 – 2.49 (m, 1H), 2.15 (dt, *J* = 13.6, 4.3 Hz, 1H), 1.72 (dt, *J* = 7.7, 4.0 Hz, 2H), 0.76 (s, 3H).$^{13}$C NMR (151 MHz, $CDCl_3$): δ 149.0, 137.5, 135.7, 128.5, 127.8, 127.6, 118.0, 109.0, 78.2, 75.3, 73.8, 48.0, 42.3, 29.9, 29.8, 17.2. HRMS: (DART) calculated for $C_{18}H_{25}O_2$ ($[M+H]^+$): 273.18545, found: 273.18427

***Analysis of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry of the cross-coupling was

determined by NOESY analysis. The following NOEs were observed:



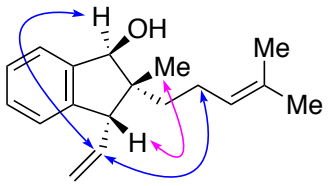



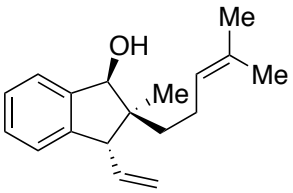

**(1*S*,2*R*,3*R*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinyl-2,3-dihydro-1*H*-inden-1-ol.** Synthesized according to the general procedure B with (*Z*)-4,8-dimethylnona-1,3,7-triene (75 mg, 0.50 mmol) and 2-bromobenzaldehyde (92 mg, 0.50 mmol). Reaction mixture was purified by automated column chromatography (50 g column, 2 to 20% EtOAc in Hexanes) to yield the title compound as a mixture of diastereomers, reddish oil (**Run 1**: 116 mg, 65% yield, 1.8:1 d.r. **Run 2**: 128 mg, 72% y, 1.9:1 d.r.). $[\alpha]^{21}_{D}$ = – 39.96 (c = 1.00 in $CHCl_3$). IR (neat, $cm^{-1}$): 3360 (br, m), 3073 (w), 2963 (m), 2923 (m), 2855 (m), 1458 (m), 1375 (m), 1017 (m), 914 (m), 756 (s). $^1$H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 7.39 – 7.34 (m, 1H), 7.27 – 7.22 (m, 2H), 7.16 – 7.12 (m, 1H), 5.81 – 5.75 (m, 1H), 5.13 – 5.04 (m, 3H), 4.89 (d, *J* = 5.9 Hz, 1H), 3.51 (d, *J* = 9.4 Hz, 1H), 2.10 – 1.96 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.49 (t, *J* = 8.4 Hz, 2H), 1.04 (s, 3H). Minor diastereomer: δ 7.39 – 7.33 (m, 1H), 7.29 – 7.21 (m, 2H), 7.09 (d, *J* = 7.0 Hz, 1H), 5.86 – 5.78 (m, 1H), 5.28 (dd, *J* = 10.1, 2.1 Hz, 1H), 5.22 (dd, *J* = 17.1, 2.0 Hz, 1H), 5.18 (t, *J* = 7.3 Hz, 1H), 4.91 (d, *J* = 7.4 Hz, 1H), 3.37 (d, *J* = 9.3 Hz, 1H), 2.25 – 2.10 (m, 2H), 1.72 (s, 3H), 1.65 (s, 3H), 1.71 – 1.55 (m, 2H), 0.81 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 144.2, 143.6, 137.5, 131.4, 128.2, 127.2, 125.2, 124.9, 124.3,

116.4, 81.4, 58.5, 50.9, 36.0, 25.7, 23.3, 18.9, 17.6. HRMS: (DART) calculated for $C_{18}H_{23}$ ($[M+H-H_2O]^+$): 239.1794, found: 239.1799

***Analysis of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry of the cross-coupling was determined by NOESY analysis. The following NOEs were observed:



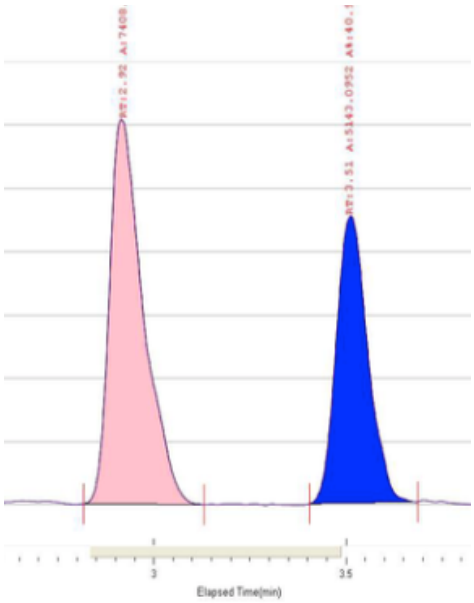

**(1*S*,2*S*,3*R*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinyl-2,3-dihydro-1*H*-inden-1-ol**. Synthesized according to the general procedure B with (*E*)-4,8-dimethylnona-1,3,7-triene (75 mg, 0.50 mmol) and 2-bromobenzaldehyde (92 mg, 0.50 mmol). Reaction mixture was purified by automated column chromatography (50 g column, 1 to 10% EtOAc in Hexanes) to yield the title compound as a mixture of diastereomers, reddish oil (**Run 1**: 155 mg, 83% yield, 6.8:1 d.r. **Run 2**: 129 mg, 69% yield, 6.8:1 d.r.). $[\alpha]^{21}_D = -29.97$ (c = 1.00 in $CHCl_3$). IR (neat, $cm^{-1}$): 3360 (br), 3072 (w), 2962 (m), 2923 (m), 2855 (m), 1458 (m), 1375 (m), 1017 (m), 914 (m), 756 (s). $^1H$ NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 7.40 (d, *J* = 7.2 Hz,

1H), 7.31 – 7.22 (m, 2H), 7.12 (d, *J* = 7.2 Hz, 1H), 5.77 (dt, *J* = 16.8, 9.7 Hz, 1H), 5.29 – 5.21 (m, 3H), 4.65 (s, 1H), 3.62 (d, *J* = 9.4 Hz, 1H), 2.12 (q, *J* = 7.9 Hz, 2H), 1.84 – 1.73 (m, 1H), 1.72 (s, 3H), 1.66 (s, 3H), 1.56 – 1.48 (m, 1H), 0.84 (s, 3H). Minor diastereomer: δ 7.42 (*d*, J = 7.2 Hz) 7.31 – 7.22 (m, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 5.98 (ddd, *J* = 16.7, 10.0, 8.9 Hz, 1H), 5.18 – 5.12 (m, 1H), 5.08 – 4.98 (m, 2H), 4.59 (s, 1H), 3.29 (d, *J* = 8.8 Hz, 1H), 2.05 – 1.98 (m, 2H), 1.69 (s, 3H), 1.68 – 1.60 (m, 1H) 1.61 (s, 3H), 1.18 – 1.12 (m, 1H), 1.02 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ δ 145.3, 143.8, 140.3, 136.5, 131.7, 128.5, 127.1, 125.1, 125.0, 118.5, 81.9, 57.3, 50.6, 34.5, 25.7, 23.3, 19.2, 17.6. HRMS: (DART) calculated for $C_{18}H_{23}$ ($[M+H–H_2O]^+$): 239.1794, found: 239.1794

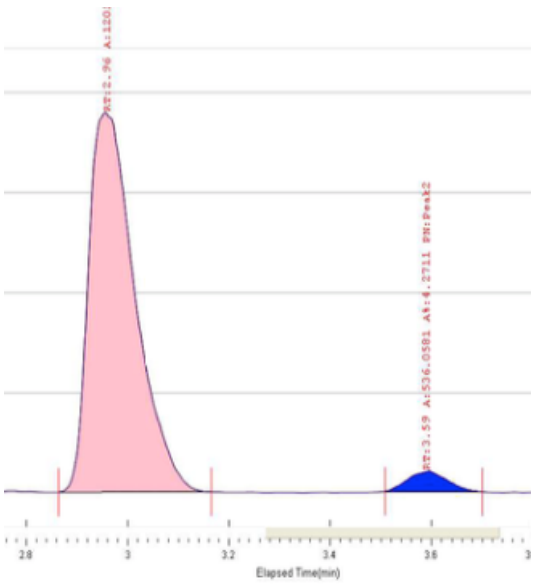
***Analysis of Stereochemistry***

The enantioselectivity was determined by SFC analysis of the reaction product. A mixture of the products resulting from use of (*R,R*)-**L4.2** and (*S,S*)- **L4.2** as the ligands in the diboration reaction were used to determine separation conditions.

*Chiral SFC (OD-H, Chiraldex, 5 mL/min, 5% i-PrOH, 100 bar, 35 °C)*



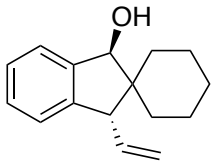

*Racemic*




*Reaction Product*

**Peak Info**

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---|---|---|---|---|---|
| 1 | 95.7289 | 12014.9083 | 2.96 | 1897.5202 | 0.0029 |
| 2 | 4.2711 | 536.0581 | 3.59 | 101.5261 | 0.0035 |
| Total: | 100 | 12550.9664 | | | |

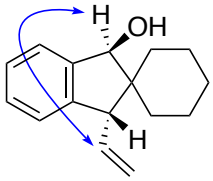


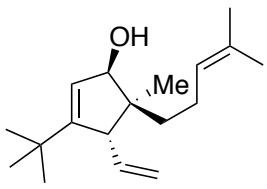

**(1'*S*,3'*R*)-3'-vinyl-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-1'-ol .** Synthesized according to the general procedure B with allylidenecyclohexane (61 mg, 0.50 mmol) and 2-bromobenzaldehyde (61 mg, 0.50 mmol). Reaction mixture was purified by automated column chromatography (50 g column, 2 to 16% EtOAc in Hexanes) to yield the title compound as a mixture of diastereomers, yellow oil (**Run 1**: 56 mg, 49% yield, 3.5:1 d.r. **Run 2**: 79 mg, 69% yield, 3.3:1 d.r.) $[\alpha]^{21}_{D}$ = – 40.252 (c = 1.545 in $CHCl_3$). IR (neat, $cm^{-1}$): 3369 (br), 2923 (s), 2853 (m), 1507 (m), 1451 (m), 1203 (m), 1015 (m), 975 (m), 750 (s). $^1$H NMR (500 MHz,

$CDCl_3$): Major diastereomer: δ 7.40 – 7.35 (m, 1H), 7.29 – 7.19 (m, 2H), 7.14 – 7.06 (m, 1H), 5.83 – 5.64 (m, 1H), 5.17 (dd, *J* = 10.1, 2.1 Hz, 1H), 5.15 – 5.09 (m, 1H), 4.92 (d, *J* = 6.7 Hz, 1H), 3.60 (d, *J* = 9.3 Hz, 1H), 1.86 – 1.04 (m, 11H). Minor diastereomer: δ 7.46 – 7.40 (m, 1H), 7.30 – 7.16 (m, 2H), 7.14 – 7.08 (m, 1H), 5.98 (ddd, *J* = 17.0, 10.2, 8.6 Hz, 1H), 5.02 – 4.92 (m, 2H), 4.65 (d, *J* = 6.3 Hz, 1H), 3.38 (d, *J* = 8.6 Hz, 1H), 1.86 – 1.04 (m, 11H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 144.4, 143.5, 136.5, 128.4, 127.1, 125.2, 124.7, 117.4, 79.5, 56.1, 51.1, 29.8, 29.1, 26.1, 23.1, 22.6. HRMS: (DART) calculated for $C_{16}H_{19}$ ($[M+H–H_2O]^+$): 211.1481, found: 211.1480

***Analysis of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry of the cross-coupling was determined by NOESY analysis. The following NOEs were observed:



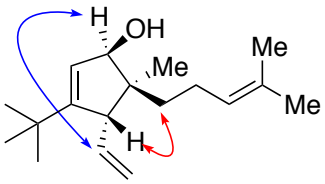



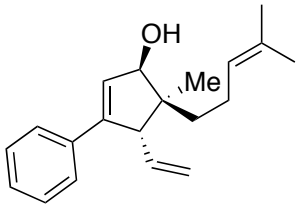

**(1*R*,4*R*,5*S*)-3-(*tert*-butyl)-5-methyl-5-(4-methylpent-3-en-1-yl)-4-vinylcyclopent-2-en-1-ol.** Synthesized according to the general procedure B with (*E*)-4,8-dimethylnona-1,3,7-triene (75 mg, 0.50

mmol) and *(Z)*-3-bromo-4,4-dimethylpent-2-enal **SI-2** (96 mg, 0.50 mmol). Reaction mixture was purified by automated column chromatography (50 g column, 2 to 16% EtOAc in Hexanes) to yield the title compound as a mixture of diastereomers, yellow oil **(Run 1**: 86 mg, 66% yield, 1.7:1 d.r. **Run 2**: 85 mg, 65% yield, 1.4:1 d.r.). $[\alpha]^{21}_{D}$ = – 21.640 (c = 2.177 in $CHCl_3$). IR (neat, $cm^{-1}$): 3349 (br), 2962 (s), 2925 (s), 2866 (m), 1458 (m), 1362 (m), 1254 (m), 1084 (m), 1009 (s), 908 (s). $^1$H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 5.75 – 5.62 (m, 1H), 5.49 – 5.46 (m, 1H), 5.15 (tt, *J* = 5.7, 1.3 Hz, 1H), 5.05 (s, 1H), 5.04 – 5.00 (m, 1H), 4.35 (dd, *J* = 7.5, 1.7 Hz, 1H), 3.11 (d, *J* = 10.2 Hz, 1H), 1.99 (q, *J* = 7.9 Hz, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.52 – 1.41 (m, 1H), 1.37 – 1.28 (m, 1H), 1.27 – 1.20 (br m, 1H), 1.06 (s, 9H), 0.92 (s, 3H). Minor diastereomer: δ 5.74 – 5.69 (m, 1H), 5.30 (s, 1H) 5.12 – 4.97 (m, 3H), 4.00 (t, *J* = 3.8 Hz, 1H), 2.76 (d, *J* = 9.8 Hz, 1H), 2.11 – 2.06 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.07 (s, 9H), 0.95 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 157.9, 139.8, 131.3, 125.2, 124.9, 116.1, 83.3, 58.6, 49.5, 34.3, 33.8, 29.5, 25.7, 23.4, 20.8, 17.6. HRMS: (DART) calculated for $C_{18}H_{29}$ ($[M+H–H_2O]^+$): 245.2264, found: 245.2276

***Analysis of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry of the cross-coupling was determined by NOESY analysis. The following NOEs were observed:



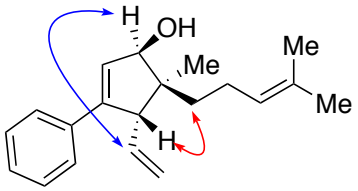



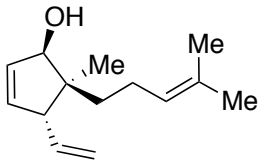

**(1*R*,4*R*,5*S*)-5-methyl-5-(4-methylpent-3-en-1-yl)-3-phenyl-4-vinylcyclopent-2-en-1-ol.** Synthesized according to the general procedure B with (*E*)-4,8-dimethylnona-1,3,7-triene (75 mg, 0.50 mmol) and *(Z)*-3-bromo-3-phenylacrylaldehyde **SI-3** (116 mg, 0.50 mmol). Reaction mixture was purified by automated column chromatography (50 g column, 2 to 16% EtOAc in Hexanes) to yield the title compound as a mixture of diastereomers, light yellow oil **(Run 1**: 96 mg, 68% yield, 1.15:1 d.r. **Run 2**: 66 mg, 47% yield, 1.7:1 d.r.). $[\alpha]^{21}_{D}$ = –50.147 (c = 2.695 in $CHCl_3$). IR (neat, $cm^{-1}$): 3378 (br), 3056 (w), 2961 (m), 2923 (m), 2854 (m), 1445 (m), 1375 (m), 1035 (m), 911 (m), 759 (s), 691 (s). $^1$H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 7.46 – 7.38 (m, 2H), 7.34 – 7.28 (m, 3H), 6.17 – 6.16 (m, 1H), 5.62 (dt, *J* = 16.9, 10.0 Hz, 1H), 5.19 – 5.15 (m, 1H), 5.14 – 5.05 (m, 2H), 4.52 – 4.43 (m, 1H), 3.54 (d, *J* = 9.5 Hz, 1H), 2.07 (q, *J* = 7.8 Hz, 2H), 1.69 (s, 3H), 1.63 (s, 3H), 1.54 – 1.47 (m, 2H), 1.45 (d, *J* = 7.0 Hz, 1H), 1.01 (s, 3H). Minor diastereomer: δ 7.54 – 7.50 (m, 2H), 7.28 – 7.22 (m, 3H), 6.39 (d, *J* = 2.9 Hz, 1H), 5.89 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1H), 5.23 – 5.19 (m, 1H), 5.16 – 5.05 (m, 2H), 4.25 – 4.15 (m, 1H), 3.21 (d, *J* = 8.7 Hz, 1H), 2.12 (q, *J* = 8.0 Hz, 2H), 1.71 (s, 3H), 1.65 (s, 3H), 1.62 – 1.56 (m, 1H), 1.37 (d, *J* = 7.6 Hz, 1H), 1.31 – 1.23 (m, 1H), 1.08 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 148.9, 140.7, 135.5, 131.4, 128.3, 128.0,

126.7, 126.6, 125.2, 116.9, 83.1, 59.6, 48.0, 33.1, 26.1, 25.7, 22.9, 17.7. HRMS: (DART) calculated for $C_{20}H_{26}$ ($[M+H-H_2O]^+$): 265.1951, found: 265.1968

***Analysis of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry of the cross-coupling was determined by NOESY analysis. The following NOEs were observed:



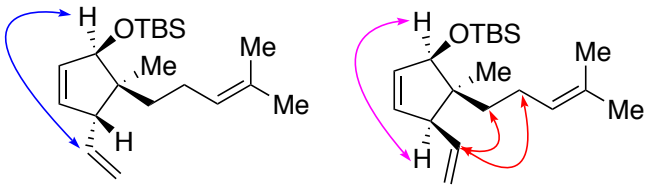




**(1*R*,4*R*,5*S*)-5-methyl-5-(4-methylpent-3-en-1-yl)-4-vinylcyclopent-2-en-1-ol (#).** Synthesized according to the general procedure B with (*E*)-4,8-dimethylnona-1,3,7-triene (75 mg, 0.50 mmol) and *(Z)*-3-iodoacrylaldehyde **SI-4** (0.50 mL, 0.50 mmol, 1.0 M in $CH_2Cl_2$). Reaction mixture was purified by automated column chromatography (50 g column, 2 to 20% EtOAc in hexanes) to yield the title compound as a mixture of diastereomers, light reddish oil **(Run 1**: 38 mg, 39% yield, 1.7:1 d.r. **Run 2**: 29 mg, 28% yield, 1.1:1 d.r.). $[\alpha]^{21}_D$ = –32.798 (c = 1.395 in $CHCl_3$). IR (neat, $cm^{-1}$): 3409 (br, m), 2962 (m), 2926 (m), 2871 (w), 1706 (m), 1452 (m), 1376 (m), 1025 (s), 915 (m), 753 (w), 700 (w). $^1$H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 5.92 (dt, *J* = 5.4, 2.5 Hz, 1H), 5.84 (dd, *J* = 6.3 Hz, 1.8 Hz,

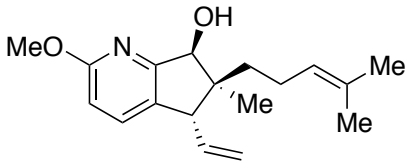
1H), 5.76 – 5.68 (m, 1H), 5.19 (ddt, *J* = 9.1, 4.8, 1.6 Hz, 1H), 5.08 – 5.06 (m, 1H), 5.05 (d, *J* = 3.3 Hz, 1H), 4.23 (dd, *J* = 7.1, 2.4 Hz, 1H), 3.12 (d, *J* = 8.5 Hz, 1H), 2.05 (q, *J* = 7.9 Hz, 2H), 1.70 (s, 3H), 1.63 (s, 3H), 1.62 – 1.57 (m, 1H), 1.53 – 1.44 (m, 1H), 1.29 (d, *J* = 7.1 Hz, 1H), 0.84 (s, 3H). Minor diastereomer: δ 5.98 – 5.95 (m, 1H), 5.91 (dd, *J* = 5.8, 2.9 Hz, 1H), 5.77 (ddd, *J* = 16.5, 10.7, 8.4 Hz, 1H), 5.20 – 5.14 (m, 1H), 5.01 (s, 1H), 5.0 – 4.97 (m, 1H), 4.06 (dd, *J* = 7.7, 2.8 Hz, 1H), 2.74 (dd, *J* = 8.6, 2.5 Hz, 1H), 2.06 (q, *J* = 7.8 Hz, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.55 – 1.47 (m, 1H), 1.44 – 1.36 (m, 1H), 1.15 (d, *J* = 7.7 Hz, 1H), 1.00 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 137.7, 137.2, 132.6, 125.1, 115.9, 83.9, 57.1, 47.5, 35.2, 25.7, 23.6, 20.5, 17.6. HRMS: (DART) calculated for $C_{14}H_{21}$ ($[M+H–H_2O]^+$): 189.1638, found: 189.1633

***Analysis of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry of the cross-coupling was determined by NOESY analysis of the TBS protected ether of the title compound. The following NOEs were observed:



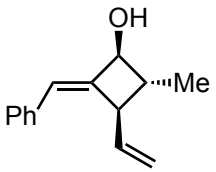

major diastereomer minor diastereomer




**(5*R*,6*S*,7*S*)-2-methoxy-6-methyl-6-(4-methylpent-3-en-1-yl)-5-vinyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-7-ol .** Synthesized according to the general procedure B with (*E*)-4,8-dimethylnona-1,3,7-triene (75 mg, 0.50 mmol) and 3-bromo-6-methoxypicolinaldehyde **SI-5** (108 mg, 0.50 mmol). Reaction mixture was purified by automated column chromatography (50 g column, 5 to 40% EtOAc in hexanes) to yield the title compound as a mixture of diastereomers, light yellow oil (**Run 1**: 54 mg, 37% yield, 2.8:1 d.r. **Run 2**: 44 mg, 31% yield, 3.3:1 d.r.). $[\alpha]^{21}_{D}$ = – 23.775 (c = 1.63 in $CHCl_3$). IR (neat, $cm^{-1}$): 3431 (br, m), 2963 (m), 2926 (m), 2858 (w), 1719 (w), 1636 (m), 1579 (m), 1474 (s), 1420 (m), 1304 (s), 1028 (m), 824 (m), 773 w). $^1$H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ $^1$H NMR (600 MHz, Chloroform-d) δ 7.33 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 5.74 (dt, *J* = 16.9, 9.6 Hz, 1H), 5.30 – 5.14 (m, 3H), 4.55 (d, *J* = 4.1 Hz, 1H), 3.94 (s, 3H), 3.53 (d, *J* = 9.2 Hz, 1H), 2.22 – 2.15 (m, 1H) 2.08 (q, *J* = 7.8 Hz, 2H), 1.78 (dt, *J* = 13.6, 8.2 Hz, 1H), 1.70 (s, 3H), 1.63 (s, 3H), 1.48 (dt, *J* = 13.3, 7.9 Hz, 1H), 0.93 (s, 3H). Minor diastereomer: δ 7.37 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 5.88 (dt, *J* = 16.8, 9.6 Hz, 1H), 5.15 – 5.02 (m, 3H), 4.49 (d, *J* = 3.9 Hz, 1H), 3.94 (s, 3H), 3.20 (d, *J* = 9.1 Hz, 1H), 2.28 (d, *J* = 6.8 Hz, 1H), 2.01 – 1.91 (m, 2H), 1.67 (s, 3H), 1.64 – 1.56 (m, 1H), 1.59 (s, 3H), 1.48 (dt, *J* = 13.3, 7.9 Hz, 1H), 1.09 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 164.5, 160.8, 136.3, 135.9, 131.6, 130.5, 124.9, 118.2, 110.3, 81.4, 54.8, 53.6, 49.3, 34.4, 25.7, 23.3, 19.6, 17.6. HRMS: (DART) calculated for $C_{18}H_{26}NO_2$ ($[M+H]^+$): calculated: 288.1958, found: 288.1970

***Analysis of Stereochemistry:***

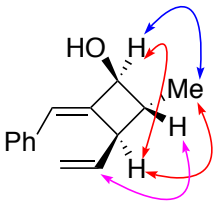
The absolute stereochemistry and relative stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh.

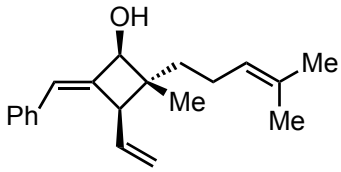



**(1*S*,3*R*,4*R*)-2-((*E*)-benzylidene)-4-methyl-3-vinylcyclobutan-1-ol.** Synthesized according to the general procedure B with (*Z*)-penta-1,3-diene (68 mg, 1.0 mmol) and (*Z)*-2-bromo-3-phenylacrylaldehyde (105 mg, 0.50 mmol), the allylation was performed at room temperature for 48 h. Reaction mixture was purified by silica gel chromatography (1 to 10% EtOAc in hexanes) to yield the title compound as a mixture of diastereomers, light yellow oil (**Run 1**: 50 mg, 50% yield, 8:1 d.r. **Run 2**: 55 mg, 55% yield, 9.6:1 d.r.). $R_f$ = 0.30 (5:1 Hex:EtOAc, stain in PMA). $[\alpha]^{21}_D$ = 88.20 (c = 1.00 in $CHCl_3$). IR (neat, $cm^{-1}$): 3418 (br, m), 3077 (w), 3059 (w), 3026 (m), 2925 (m), 2869 (m), 1737 (w), 1493 (m), 1322 (m), 1207 (m), 966 (w), 627 (s). $^1$H NMR (600 MHz, $CDCl_3$): Major diastereomer: δ 7.31 – 7.29 (m, 1H), 7.26 – 2.24 (m, 3H), 7.19 – 7.16 (m, 1H), 6.52 (t, *J* = 2.3 Hz, 1H), 5.64 (ddd, *J* = 17.2, 10.0, 8.5 Hz, 1H), 5.10 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.96 (dd, *J* = 10.1, 1.7 Hz, 1H), 4.25 (dd, *J* = 6.0, 2.0 Hz, 1H), 3.08 (dt, *J* = 8.2, 2.5 Hz, 1H), 2.00 (dt, *J* = 14.6, 6.8 Hz, 1H), 1.26 (d, *J* = 6.7 Hz, 3H). Minor diastereomer: 5.93 (ddd, *J* = 17.1, 10.2, 6.9 Hz), 5.28 – 5.14 (m, 2H), 4.42 (dt, *J* = 7.5, 2.8 Hz, 1H), 3.69 (d, *J* = 8.2 Hz, 1H), 2.39 (dt, *J* = 9.9, 7.2 Hz), 1.15 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (151 MHz, $CDCl_3$): δ 148.5, 137.7, 135.3, 129.1, 127.9, 126.8, 121.7, 115.3, 76.3, 48.9, 47.2, 17.2. HRMS: (DART) calculated for $C_{14}H_{15}$ ($[M+H–H_2O]^+$): calculated:183.1174, found: 183.1175.

***Analysis of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry of the cross-coupling was determined by NOESY analysis. The following NOEs were observed:



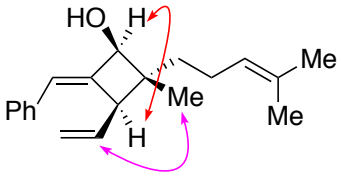



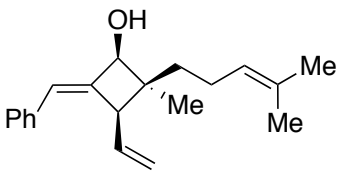

**(1*S*,2*R*,3*R*)-4-((*E*)-benzylidene)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclobutan-1-ol**. Synthesized according to the general procedure B with (*Z*)-4,8-dimethylnona-1,3,7-triene (75 mg, 0.50 mmol) and (*Z*)-2-bromo-3-phenylacrylaldehyde (105 mg, 0.50 mmol), allylation allowed to run for 48 h. Reaction mixture was purified first by automated column chromatography (50 g column, 5 to 15% EtOAc in hexanes). A second silica gel chromatography was performed (100% DCM) to yield the title compound as a mixture of diastereomers, light yellow oil (**Run 1**: 67 mg, 48% yield, 7.0:1 d.r. **Run 2**: 73 mg, 52% yield 7.2:1 d.r.). $R_f$ = 0.27 (5:1 Hex:EtOAc, stain in PMA). $[\alpha]^{21}_D$ = 20.125 (c = 0.97, $CHCl_3$). IR (neat, $cm^{-1}$): 3516 (br, m), 3253 (m), 3027 (m), 2928 (w), 1725 (m), 1449 (s), 1376 (m),

1214 (m), 672 (s). $^{1}$H NMR (600 MHz, $CDCl_3$): Major diastereomer: δ 6.54 (t, *J* = 2.4 Hz, 1H), 5.47 (ddd, *J* = 17.2, 10.1, 9.1 Hz, 1H), 5.18 – 5.12 (m, 1H), 5.08 – 5.04 (m, 2H), 4.39 (dd, *J* = 8.9, 2.1 Hz, 1H), 3.28 (dd, *J* = 9.0, 2.7 Hz, 1H), 2.05 – 2.02 (m, 2H), 1.75 (d, *J* = 9.0 Hz, 1H), 1.72 – 1.68 (m, 2H), 1.63 (s, 3H), 1.60 (s, 3H), 0.91 (s, 3H). $^{13}$C NMR (151 MHz, $CDCl_3$): δ 146.3, 135.4, 135.3, 131.6, 129.2, 127.8, 126.7, 124.6, 122.4, 117.8, 76.9, 51.9, 47.5, 41.6, 25.7, 23.1, 17.6, 13.5. HRMS: (DART) calculated for $C_{20}H_{27}O$ ($[M+H]^+$): calculated 283.2062, found: 283.2075.

***Analysis of Stereochemistry:***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry of the cross-coupling was determined by NOESY analysis. The following NOEs were observed:



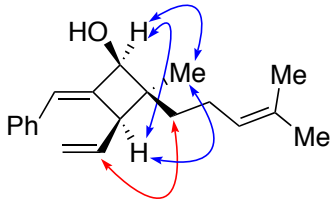




**(1*S*,2*S*,3*R*)-4-((*E*)-benzylidene)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclobutan-1-ol.** Synthesized according to the general procedure B with (*E*)-4,8-dimethylnona-1,3,7-

triene (75 mg, 0.50 mmol) and (*Z*)-2-bromo-3-phenylacrylaldehyde (105 mg, 0.50 mmol), allylation allowed to run for 48 h. Reaction mixture was purified first by silica gel chromatography (0 to 10% EtOAc in hexanes). A second silica gel chromatography was performed (100% DCM) to yield the title compound as a mixture of diastereomers, light yellow oil (**Run 1**: 54 mg, 38% yield, 4.4:1 d.r. **Run 2**: 47 mg, 33% yield 3.8:1 d.r.). $R_f$ = 0.27 (5:1 Hex:EtOAc, stain in PMA). $[\alpha]^{21}_D$ = 41.265 (c = 0.97, $CHCl_3$). IR (neat, $cm^{-1}$): 3491 (br, m), 3027 (m), 2966 (s), 2854 (m), 1725 (m), 1493 (m), 1330 (s), 1263 (m), 1071 (m), 751 (m), 696 (s). $^1$H NMR (600 MHz, $CDCl_3$): Major diastereomer: δ 7.29 – 7.24 (m, 4H), 7.20 – 7.17 (m, 1H), 6.58 (t, *J* = 2.2 Hz, 1H), 5.66 (ddd, *J* = 17.2, 10.1, 8.8 Hz, 1H), 5.16 – 5.08 (m, 3H), 4.33 (d, *J* = 5.8 Hz, 1H), 3.26 (dd, *J* = 8.8, 2.4 Hz, 1H), 2.06 – 2.00 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.51 (ddd, *J* = 13.9, 10.7, 6.3 Hz, 1H), 1.37 (ddd, *J* = 13.9, 10.8, 5.9 Hz, 1H), 1.26 (s, 3H). $^{13}$C NMR (151 MHz, $CDCl_3$): δ 145.4, 135.6, 135.5, 131.4, 129.0, 127.9, 126.9, 125.0, 124.2, 117.5, 79.1, 54.4, 46.6, 30.5, 25.7, 24.7, 23.4, 17.7. HRMS: (DART) calculated for $C_{20}H_{27}O$ ($[M+H]^+$): calculated 283.2062, found: 283.205.

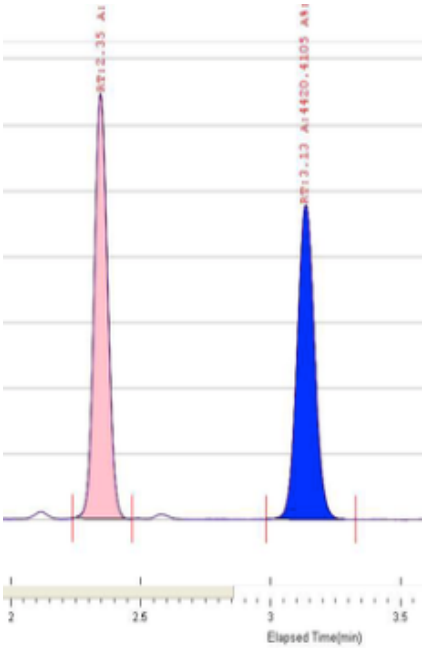
***Analysis of Stereochemistry***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*$Pr_2$TADDOL-PPh. The relative stereochemistry of the cross-coupling was determined by NOESY analysis. The following NOEs were observed:

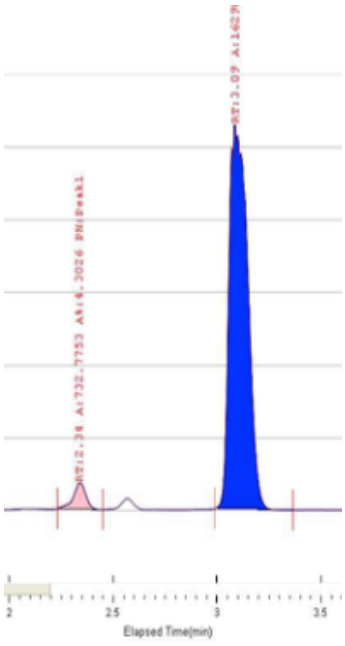



The enantioselectivity was determined by SFC analysis of the reaction product. A mixture of the products resulting from use of (*R,R*)-**L4.2** and (*S,S*)- **L4.2** as the ligands in the diboration reaction were used to determine separation conditions.

*Chiral SFC (OD-H, Chiraldex, 3 mL/min, 14% MeOH, 100 bar, 35 °C)*

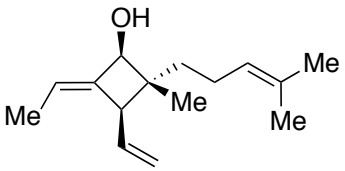



Racemic




Reaction Product

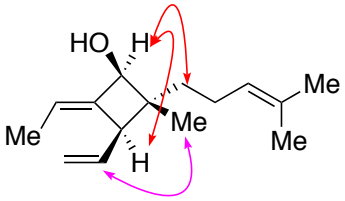
| Peak Info | | | | | |
|---|---|---|---|---|---|
| **Peak No** | **% Area** | **Area** | **RT (min)** | **Height (mV)** | **K'** |
| 1 | 4.3026 | 732.7753 | 2.34 | 181.5933 | 0.0037 |
| 2 | 95.6974 | 16298.3031 | 3.09 | 2645.8531 | 0.0049 |
| Total: | 100 | 17031.0784 | | | |



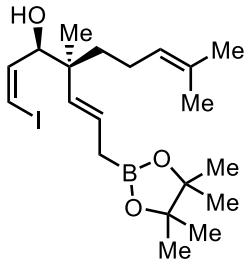

**(1*S*,2*R*,3*R*,*E*)-4-ethylidene-2-methyl-2-(4-methylpent-3-en-1-yl)-3-vinylcyclobutan-1-ol (#).** Synthesized according to the general procedure B with (*Z*)-4,8-dimethylnona-1,3,7-triene (75 mg, 0.50 mmol) and (*Z*)-2-bromobut-2-enal (74 mg, 0.50 mmol), allylation allowed to run for 48 h. Reaction mixture was purified first by automated column chromatography (50 g column, 5 to 15% EtOAc in hexanes). A second silica gel chromatography was performed (100% DCM) to yield the title compound as a mixture of diastereomers, light yellow oil (**Run 1**: 67 mg, 61% yield, 7.7:1 d.r. **Run 2**: 69 mg, 63% yield 7.9:1 d.r.). $R_f$ = 0.33 (10:1 Hex:EtOAc, stain in PMA). $[\alpha]^{21}_D$ = 29.292 (c = 0.58, $CHCl_3$). IR (neat, $cm^{-1}$): 3342 (br, m), 2965 (m), 2914 (m), 2860 (m), 1631 (w), 1448 (m), 1376 (m), 1099 (m), 996 (m), 911 (s). $^1$H NMR (600 MHz, $CDCl_3$): Major diastereomer: δ 5.78 (dt, *J* = 17.1, 9.7 Hz, 1H), 5.55 (ddd, *J* = 9.1, 6.9, 4.6 Hz, 1H), 5.13 – 5.04 (m, 3H), 4.15 (s, 1H), 2.93 (d, *J* = 9.5 Hz, 1H), 1.98 (q, *J* = 7.3 Hz, 2H), 1.68 (s, 3H), 1.60 (s, 6H), 1.52 – 1.52 (m, 2H), 0.90 (s, 3H). $^{13}$C NMR (151 MHz, $CDCl_3$): δ 144.0, 136.6, 131.4, 124.7, 117.2, 116.7, 76.4, 50.7, 46.6, 41.5, 25.7, 23.0, 17.6, 13.3, 12.8. HRMS: (DART) calculated for $C_{15}H_{23}$ ([M+H-$H_2O$]$^+$): calculated 203.1800, found: 203.1801.

***Analysis of Stereochemistry***

The absolute stereochemistry was assigned by analogy to other products derived from (*R,R*)-*i*Pr$_2$TADDOL-PPh. The relative stereochemistry of the cross-coupling was determined by NOESY analysis. The following NOEs were observed:

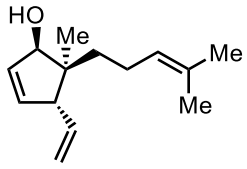



### 4.7.4 Experimental Procedures for Steriod Synthesis




In an argon-filled glovebox, charged an oven-dried 50 mL RB flask with $B_2pin_2$ (2.21 g, 8.70 mmol), **L4.2** (271 mg, 0.298 mmol), $Pt(dba)_3$ (224 mg, 0.249 mmol), and toluene (8.3 mL). Sealed and brought the vial to a fume hood to heat at 80 °C in an oil bath for 20 min, then returned the flask to the glovebox, added (*E*)-4,8-dimethylnona-1,3,7-triene (1.245 g, 1.50 mL, 8.29 mmol), and resealed. Brought the flask to the hood to heat at 60 °C for

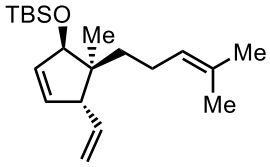
24 h, at which point, added (*Z*)-3-iodoacrylaldehyde as a 1.13 M solution in DCM (8.1 mL, 9.12 mmol) and stirred at 60 °C for 14 h. Removed the flask from heat and concentrated on a rotary evaporator. Crude reaction mixture was purified by automated column chromatography (100 g column, 3 to 30% EtOAc in hexanes) to yield the title compound as a dark amber oil (3.10 g, 6.74 mmol, 81% yield). IR (neat, $cm^{-1}$): 3478 (br, m), 2975 (m), 2926 (w), 1451 (w), 1371 (m), 1349 (m), 1323 (m), 1142 (s), 967 (m), 848 (w), 594 (w). $^{1}H$ NMR (500 MHz, $CDCl_3$): δ 6.44 (d, *J* = 7.6 Hz, 1H), 6.18 – 6.12 (m, 1H), 5.52 (dt, *J* = 15.4, 7.6 Hz, 1H), 5.34 – 5.27 (m, 1H), 5.09 – 5.04 (m, 1H), 4.02 (d, *J* = 8.7 Hz, 1H), 2.25 (d, *J* = 3.4 Hz, 1H), 1.88 (ddd, *J* = 16.4, 10.8, 7.3 Hz, 2H), 1.78 – 1.69 (m, 2H), 1.65 (s, 3H), 1.56 (s, 3H), 1.45 (ddd, *J* = 13.5, 11.2, 5.4 Hz, 1H), 1.32 (ddd, *J* = 13.4, 11.1, 6.1 Hz, 1H), 1.22 (s, 12H), 0.98 (s, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 140.18, 134.92, 131.17, 127.81, 125.05, 85.28, 83.56, 79.33, 45.24, 37.69, 25.80, 24.90, 24.88, 22.91, 17.82, 17.41, 16.75. HRMS: (DART) calculated for $C_{20}H_{33}BIO_2$ ($[M+H–H_2O]^+$): 443.1613, found: 443.1551




In an argon-filled glovebox, charged a 350 mL (outer volume) pressure flask with allylboronate X (3.10 g, 6.74 mmol) and THF (50 mL). Added tri-*tert*-butylphopshine as a 10 wt% solution in hexane (2.0 mL, 1.36 g, 0.674 mmol), $Pd(OAc)_2$ (76 mg, 0.34 mmol), and CsF (3.07 g, 20.2 mmol). Sealed and brought to the fume hood to heat at 65 °C for

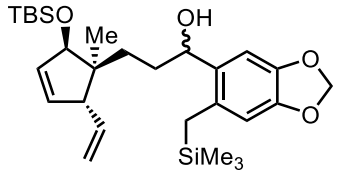
16 h. Allowed to cool, then added water (100 mL) and diluted with EtOAc. Extracted three times with EtOAc, then dried, filtered, and concentrated to a brown oil. Crude reaction mixture was purified by automated column chromatography (100 g column, 2 to 30% EtOAc in hexanes) to yield the title compound as an amber oil as a 10:1 mixture of diastereomers (910 mg, 4.4 mmol, 65% yield).

See characterization data above.




Charged a flame-dried 200 mL RB flask with alcohol X (910 mg, 4.41 mmol) and imidazole (600 mg, 8.82 mmol). Dissolved in DCM (20 mL) and then added TBSCl (1.33 g, 8.82 mmol) as a solution in DCM (10 mL). Stirred overnight. Quenched with $H_2O$ and extracted three times with DCM. Dried, filtered, and concentrated to a yellow oil. Crude reaction mixture was purified by automated column chromatography (100 g column, 0.25 to 2% EtOAc in hexanes) to yield the title compound as a clear, colorless liquid (1.044 g, 3.257 mmol, 74% yield). $[\alpha]^{21}_{D}$ = – 171.44 (c = 1.305, $CHCl_3$). IR (neat, $cm^{-1}$): 3059 (w), 2957 (m), 2928 (m), 2884 (m), 2856 (m), 1637 (w), 1462 (w), 1361 (m), 1063 (s), 938 (w), 891 (m), 834 (s), 772 (s), 672 (w). $^1$H NMR (500 MHz, $CDCl_3$): δ 5.81 – 5.57 (m, 3H), 5.10 (t, *J* = 7.0 Hz, 1H), 5.06 – 4.95 (m, 2H), 4.30 – 4.27 (m, 1H), 3.11 (d, *J* = 8.5 Hz, 1H), 2.05 – 1.85 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.56 – 1.52 (m, 1H), 1.40 (td, *J* = 12.8, 5.1 Hz, 1H), 0.88 (s, 9H), 0.84 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H). $^{13}$C NMR (151 MHz, $CDCl_3$): δ 138.1, 135.8, 133.3, 130.6,

125.7, 115.3, 84.0, 56.9, 48.2, 35.8, 25.9, 25.7, 23.8, 21.0, 18.2, 17.7, -4.0, -4.8. HRMS: (DART) calculated for $C_{20}H_{37}OSi$ ($[M+H]^+$): 321.2614, found: 321.2629



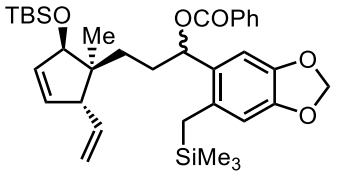

For the conversion of the side-chain prenyl group to an aldehyde, followed a two-step procedure developed by Leighton and coworkers.[88] Cooled a solution of TBS ether (1.04 g, 3.24 mmol) in DCM (10 mL) to -10 °C, then added a solution of *m*CPBA (XX) in DCM (5 mL) over 1 h via syringe pump. Stirred for 2 h at -10 °C, then 1 h at room temperature. Quenched with 2 M KOH and extracted three times with DCM. Dried, filtered, and concentrated to a clear, colorless oil.

Dissolved the crude epoxide in ether (10 mL) and added fast dropwise to a solution of periodic acid (739 mg, 3.24 mmol) in ice-cold THF (5 mL). Stirred 40 min at 0 °C, then quenched with saturated aqueous sodium bicarbonate and extracted three times with ethyl acetate. Dried, filtered, and concentrated to a colorless suspension. Redissolved in DCM, washed with brine, and extracted the brine layer twice with DCM. Dried the

[88] Plummer, C. W.; Soheili, A.; Leighton, J. L. *Org. Lett.* **2012**, *14*, 2462–2464.

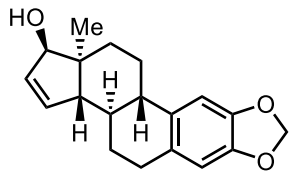
combined organics, filtered, and concentrated to a turbid, colorless oil. Dissolved the crude aldehyde in THF (10 mL) and used immediately in the next step.

Flame-dried a 100 mL Schlenk flask and charged with bromide X in THF (32 mL). Cooled to -78 °C, then added 2.5 M *n*-BuLi (2.59 mL, 6.48 mmol) dropwise. Stirred 4 h, then added the solution of aldehyde by fast dropwise addition. Stirred 48 h, allowing the bath to expire. Quenched with water and diluted with EtOAc, then extracted three times with EtOAc. Dried, filtered, and concentrated to a pale brown oil. Crude reaction mixture was purified by automated column chromatography (100 g column, 2 to 20% EtOAc in hexanes) to yield the title compound as an amber oil, a mixture of inseparable diastereomers in a 1.25:1 ratio (1.074 g, 2.13 mmol, 66% yield over three steps). $^{1}$H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 6.93 (s, 1H), 6.42 (s, 1H), 5.90 – 5.88 (m, 2H), 5.76 – 5.64 (m, 3H), 5.05 – 4.98 (m, 2H), 4.71 – 4.65 (m, 1H), 4.31 – 4.28 (m, 1H), 3.12 (d, *J* = 8.8 Hz, 1H), … 0.86 (s, 9H), 0.84 (s, 3H), 0.03 (s, 3H), 0.02 (s, 9H), 0.01 (s, 3H). Minor diastereomer: δ 6.93 (s, 1H), 6.43 (s, 1H), 5.89 – 5.88 (m, 2H), 5.76 – 5.64 (m, 3H), 5.05 – 4.98 (m, 2H), 4.71 – 4.65 (m, 1H), 4.31 – 4.28 (m, 1H), 3.08 (d, *J* = 8.8 Hz, 1H), ….. 0.89 (s, 9H), 0.83 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.02 (s, 9H). HRMS: (DART) calculated for $C_{28}H_{45}O_3Si_2$ ($[M+H–H_2O]^+$): 485.2902, found: 485.2916



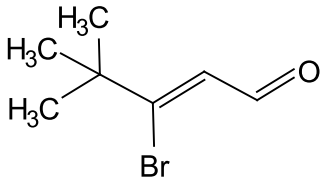

Charged a 100 mL flask with alcohol X (1.07 g, 2.13 mmol), then dissolved in pyridine (10 mL). Added benzoyl chloride (0.500 mL, 0.605 g, 4.30 mmol) and DMAP (26 mg, 0.21 mmol) and stirred 48 h. Quenched with water and diluted with DCM. Extracted three times with DCM, then washed the combined organics twice with water. Dried, filtered, and concentrated to a thick yellow oil. Ran a 100 g Biotage column, gradient from 1 to 14% EtOAc/hexanes. Isolated a clear, pale yellow oil as an inseparable mixture of diastereomers in a 1.25:1 ratio (1.21 g, 1.99 mmol, 94% yield). $[\alpha]^{21}_{D} = -92.223$ (c = 1.530, $CHCl_3$). IR (neat, $cm^{-1}$): 3060 (w), 2953 (w), 2928 (w), 2884 (w), 2855 (w), 1715 (m), 1602 (m), 1247 (s), 1068 (m), 913 (s), 709 (s). $^1$H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 8.06 – 8.03 (m, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 6.96 (s, 1H), 6.46 (s, 1H), 6.09 – 6.04 (m, 1H), 5.89 – 5.88 (m, 2H), 5.74 – 5.62 (m, 3H), 5.06 – 4.95 (m, 2H), 4.29 (s, 1H), 3.12 (d, *J* = 8.4 Hz, 1H) …. 0.85 (s, 3H), 0.82 (s, 9H), 0.03 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H). Minor diastereomer: δ 8.07 – 8.04 (m, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 6.96 (s, 1H), 6.46 (s, 1H), 6.09 – 6.04 (m, 1H), 5.91 – 5.98 (m, 2H), 5.74 – 5.62 (m, 3H), 5.06 – 4.95 (m, 2H), 4.27 (s, 1H), 3.07 (d, *J* = 8.5 Hz, 1H), … 0.84 (s, 3H), 0.83 (s, 9H), 0.04 (s, 6H), 0.01 (s, 6H). $^{13}$C NMR (151 MHz, $CDCl_3$): Major diastereomer: δ 165.8, 146.7, 144.8, 138.4, 135.3, 133.5, 132.7, 130.6, 130.4, 129.6, 128.2, 115.4, 109.0, 106.3, 100.7, 84.8, 74.3, 56.5, 47.7, 32.5, 32.1, 25.9, 23.2, 21.5, 18.1, 1.3, –4.3, –4.8. Minor diastereomer: δ 165.8, 146.7, 144.9, 138.0, 135.6, 133.3, 131.6, 130.6, 130.5, 129.7,

128.2, 115.5, 109.0, 106.5, 100.7, 84.5, 74.3, 56.8, 47.6, 32.2, 32.1, 25.8, 23.1, 21.2, 18.1, 1.29, –4.2, –4.7. HRMS: (DART) calculated for $C_{28}H_{45}O_3Si_2$ ($[M+H–PhCOOH]^+$): 485.2902, found: 485.3030.




Charged a 50 mL polypropylene centrifuge tube with tetrabutylammonium triphenylfluorosilicate (TBAT) (950 mg, 1.76 mmol), then added silane X (356 mg, 0.587 mmol) as a solution in DMF (11.7 mL). Sealed the tube and heated to 80 °C for 48 h, then allowed to cool to room temperature and added tetrabutylammonium fluoride (TBAF) as a 1 M solution in THF (0.34 mL, 1.2 mmol). Stirred at room temperature for an additional 12 h. Diluted with 100 mL water, then extracted four times with ether. Washed the combined organic layers with brine once, then dried, filtered, and concentrated to a yellow oil. Crude reaction mixture was purified by automated column chromatography (100 g column, 4 to 40% EtOAc in hexanes) to yield the title compound as a white solid (xx mg, xx mmol, 44% yield). Recrystallized from ether in order to obtain X-ray diffraction data. $[\alpha]^{21}_D$ = – 62.578 (c = 0.905, $CHCl_3$). IR (neat, $cm^{-1}$): 3361 (br, m), 3047 (w), 2924 (m), 2855 (m), 1503 (s), 1152 (w), 1118 (m), 1038 (s), 937 (w), 788 (w). $^1H$ NMR (500 MHz, $CDCl_3$): δ 6.83 (s, 1H), 6.57 (s, 1H), 6.23 (d, *J* = 6.3, 1H), 6.02 (dt, *J* = 5.9, 3.0 Hz, 1H), 5.90 – 5.87 (m, 2H), 4.15 (d, *J* = 2.6 Hz, 1H), 2.92 – 2.75 (m, 2H), 2.50 (ddd, *J* = 11.6, 3.4, 1.6 Hz,

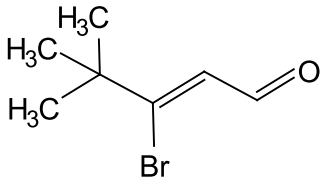
1H), 2.39 – 2.30 (m, 1H), 2.30 – 2.22 (m, 1H), 2.06 (ddt, *J* = 12.0, 5.9, 2.7 Hz, 1H), 1.96 (td, *J* = 12.4, 4.3 Hz, 1H), 1.77 – 1.54 (m, 3H), 1.48 (qd, *J* = 11.9, 6.6 Hz, 1H), 1.35 – 1.20 (br m, 1H), 0.86 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 145.86, 145.49, 137.41, 133.54, 133.36, 129.73, 108.88, 105.64, 100.71, 82.59, 77.37, 77.16, 76.95, 54.92, 46.28, 45.00, 36.09, 30.70, 29.60, 28.33, 26.17, 19.62. HRMS: (DART) calculated for $C_{19}H_{21}O_2$ ($[M+H-H_2O]^+$): 281.1542, found: 281.1553




511

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

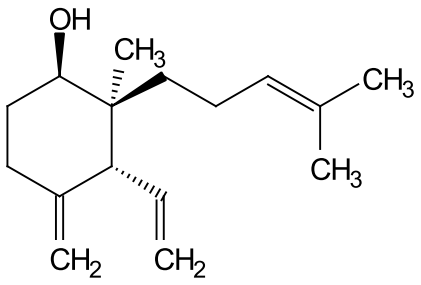
f1 (ppm)




512

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

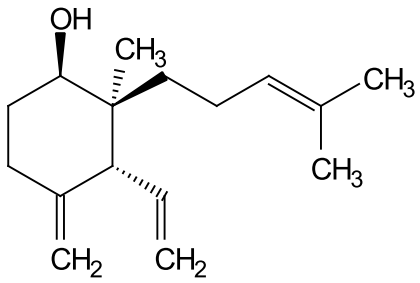
f1 (ppm)




513

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

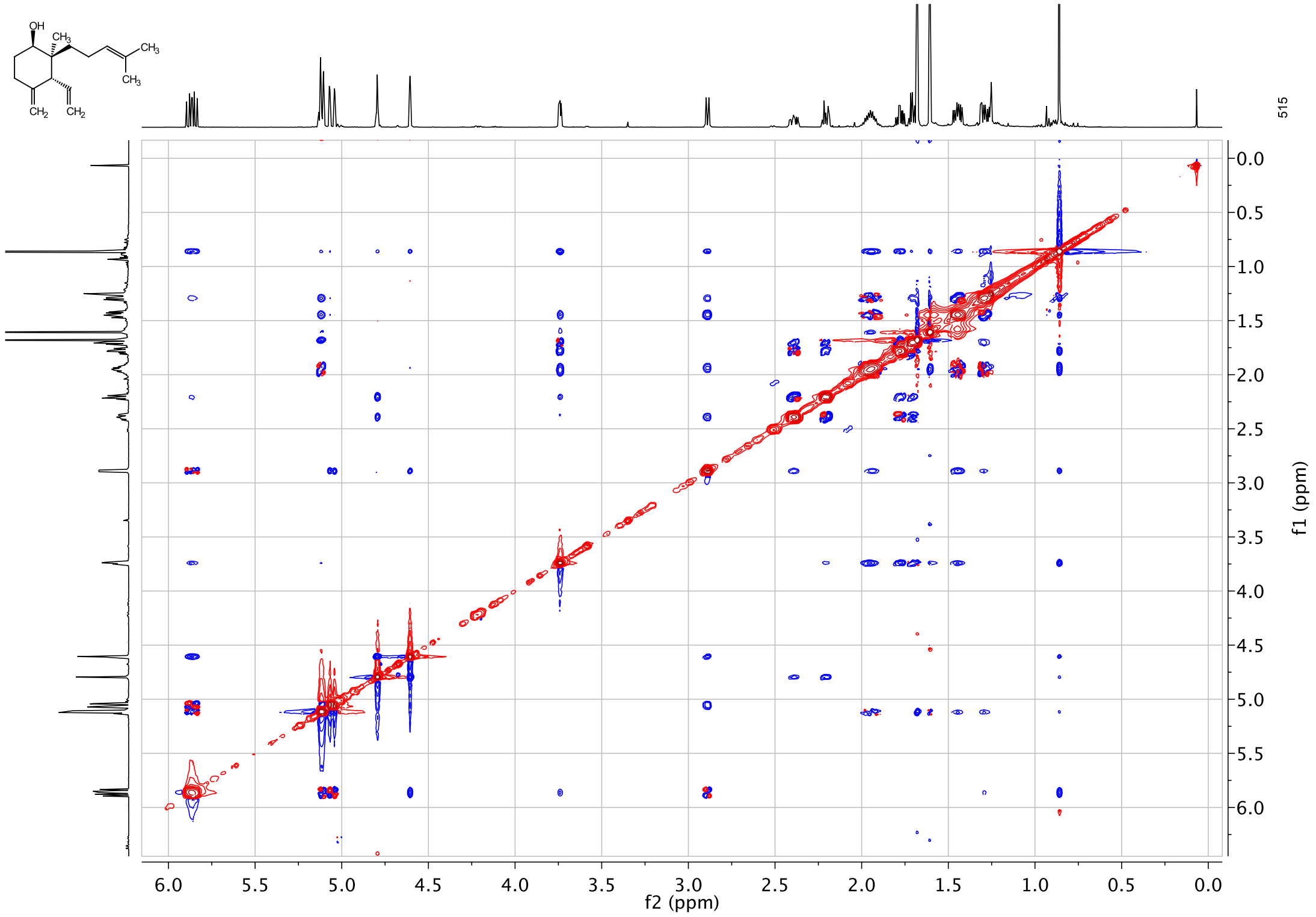
f1 (ppm)

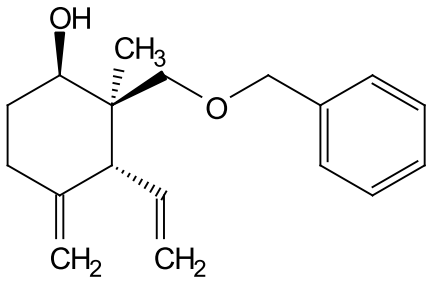



514

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

f1 (ppm)

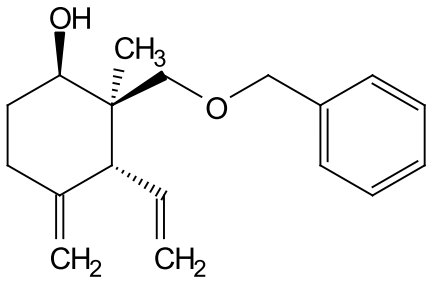

OH
CH3
CH3
CH3
CH2
CH2
515
f2 (ppm)
f1 (ppm)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0




516

4 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1

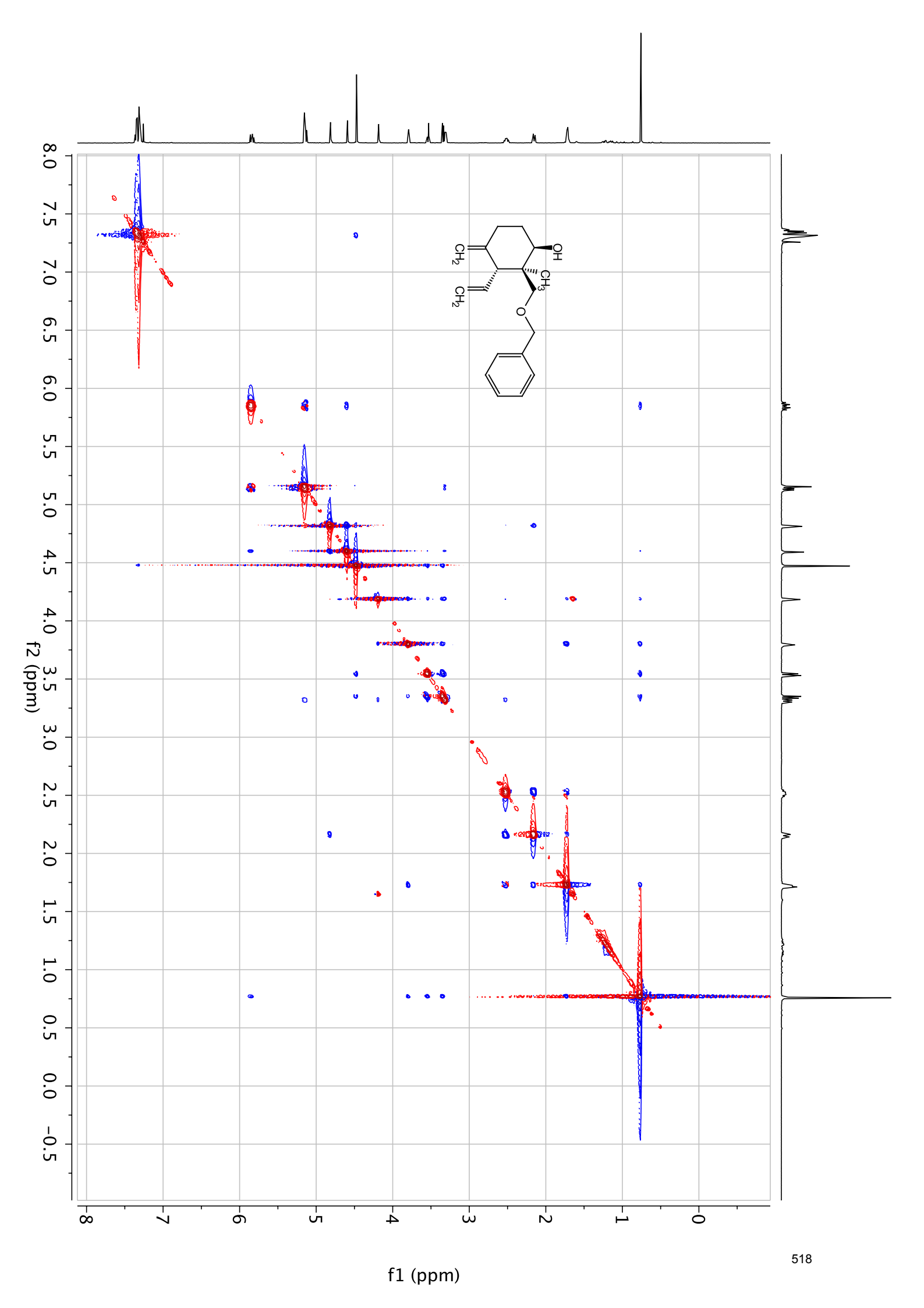
f1 (ppm)



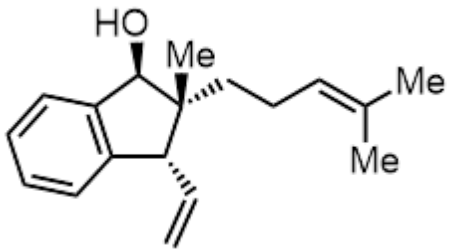

517

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)


f2 (ppm)
f1 (ppm)
CH2
CH2
CH3
OH
O

400 MHz

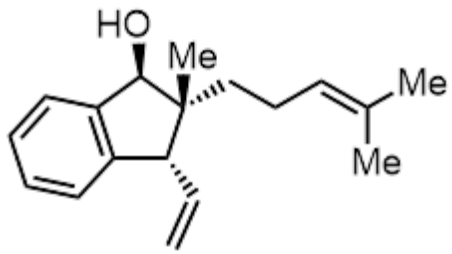



519

14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2

f1 (ppm)

400 MHz

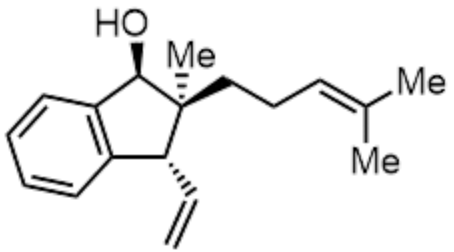



520

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

400 MHz

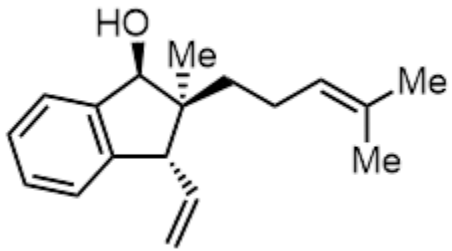



521

10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 -1.0

f1 (ppm)

400 MHz

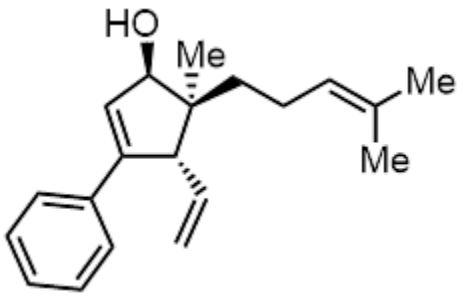



522

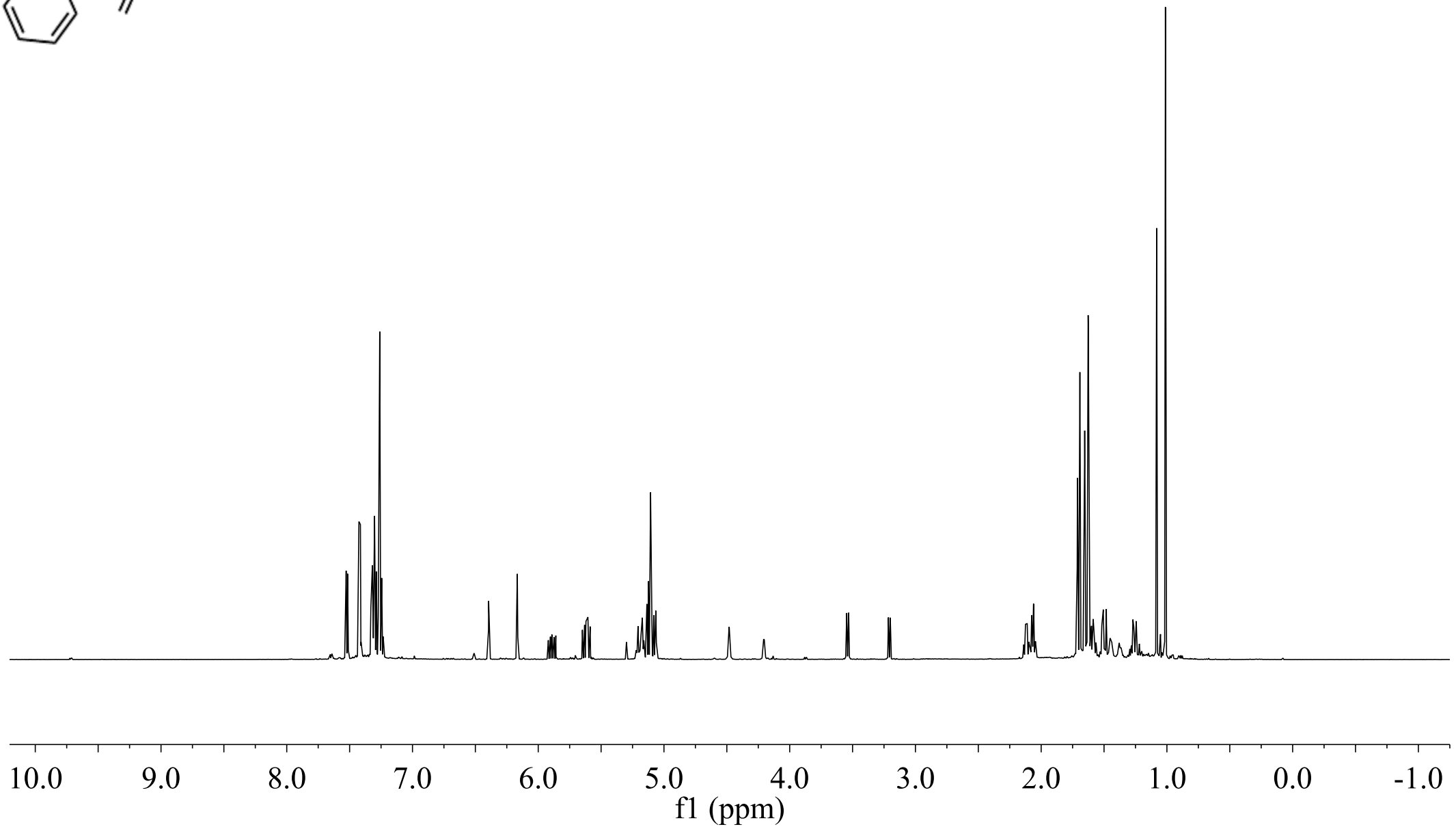
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

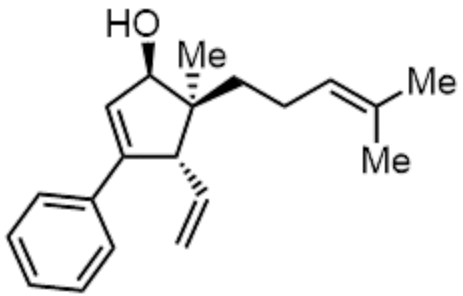
400 MHz




523



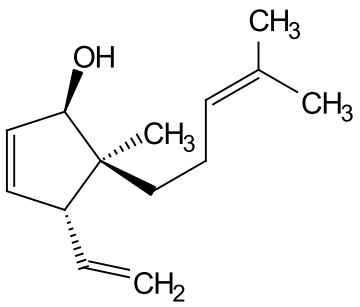
400 MHz




524

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

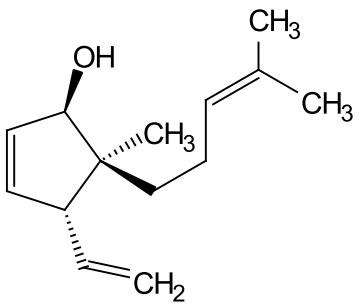
f1 (ppm)




525

4 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1

f1 (ppm)

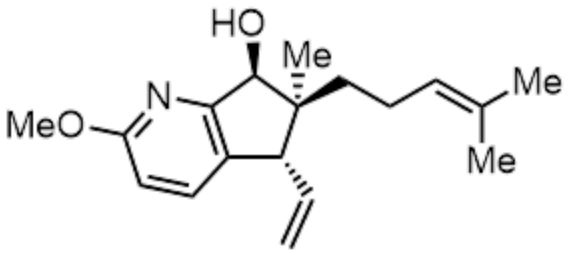



526

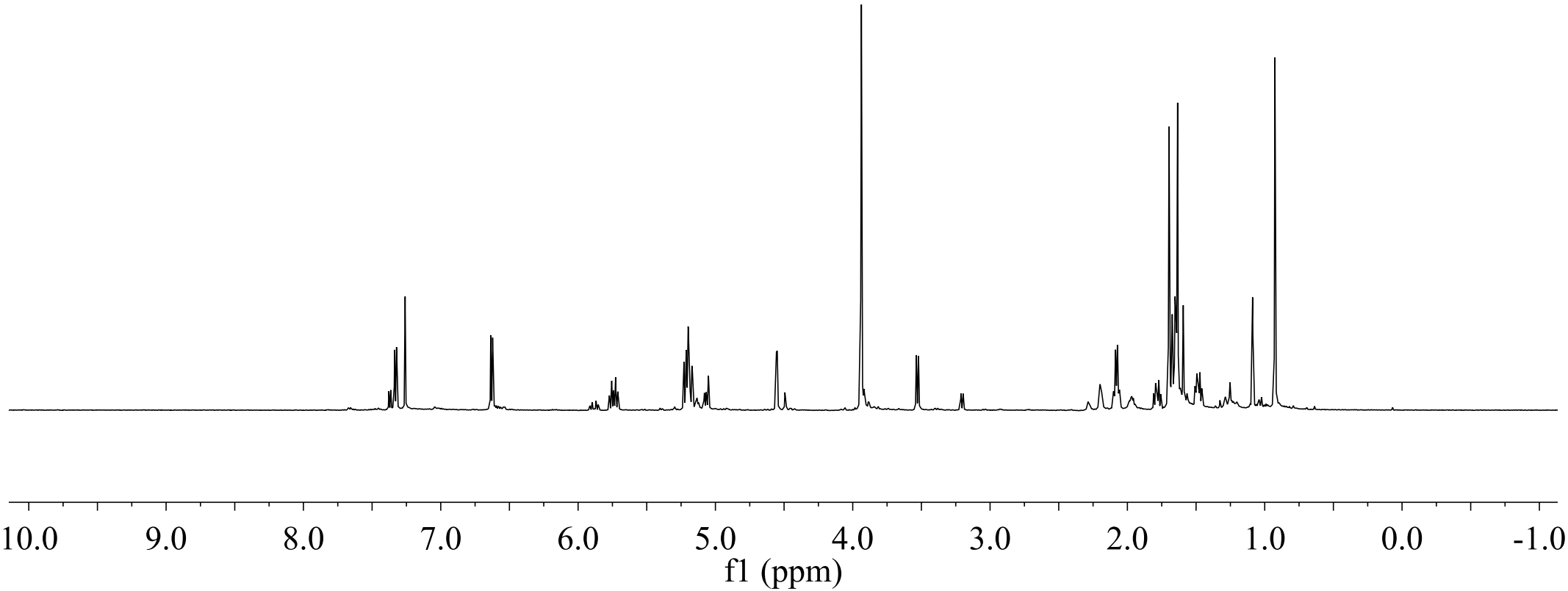
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

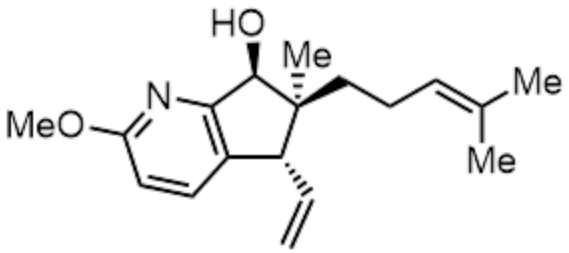
f1 (ppm)

400 MHz




527

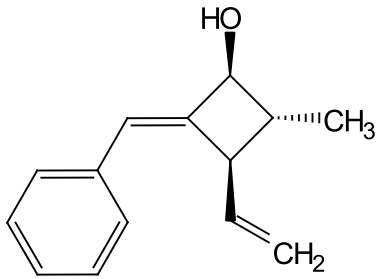





528

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

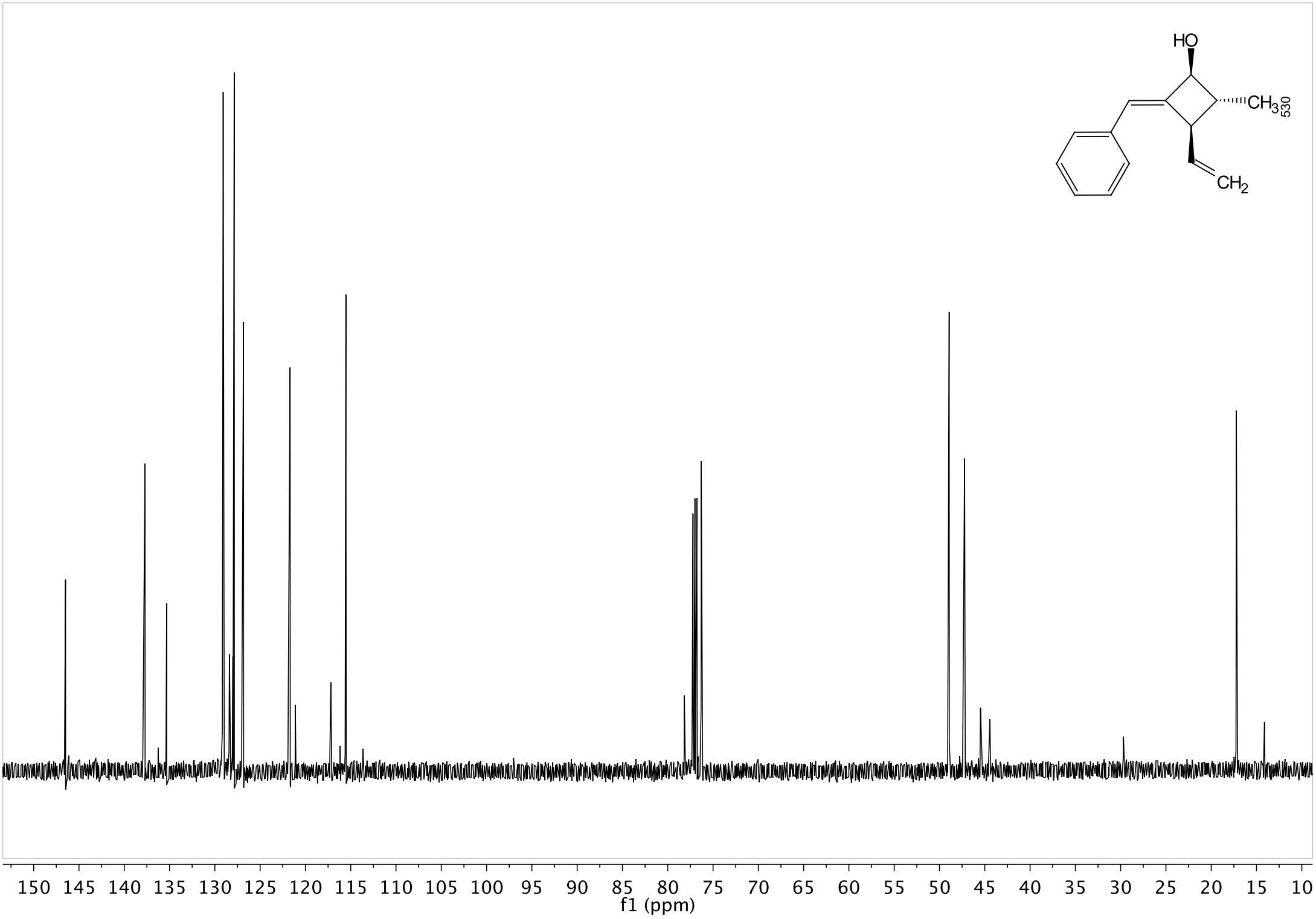
f1 (ppm)

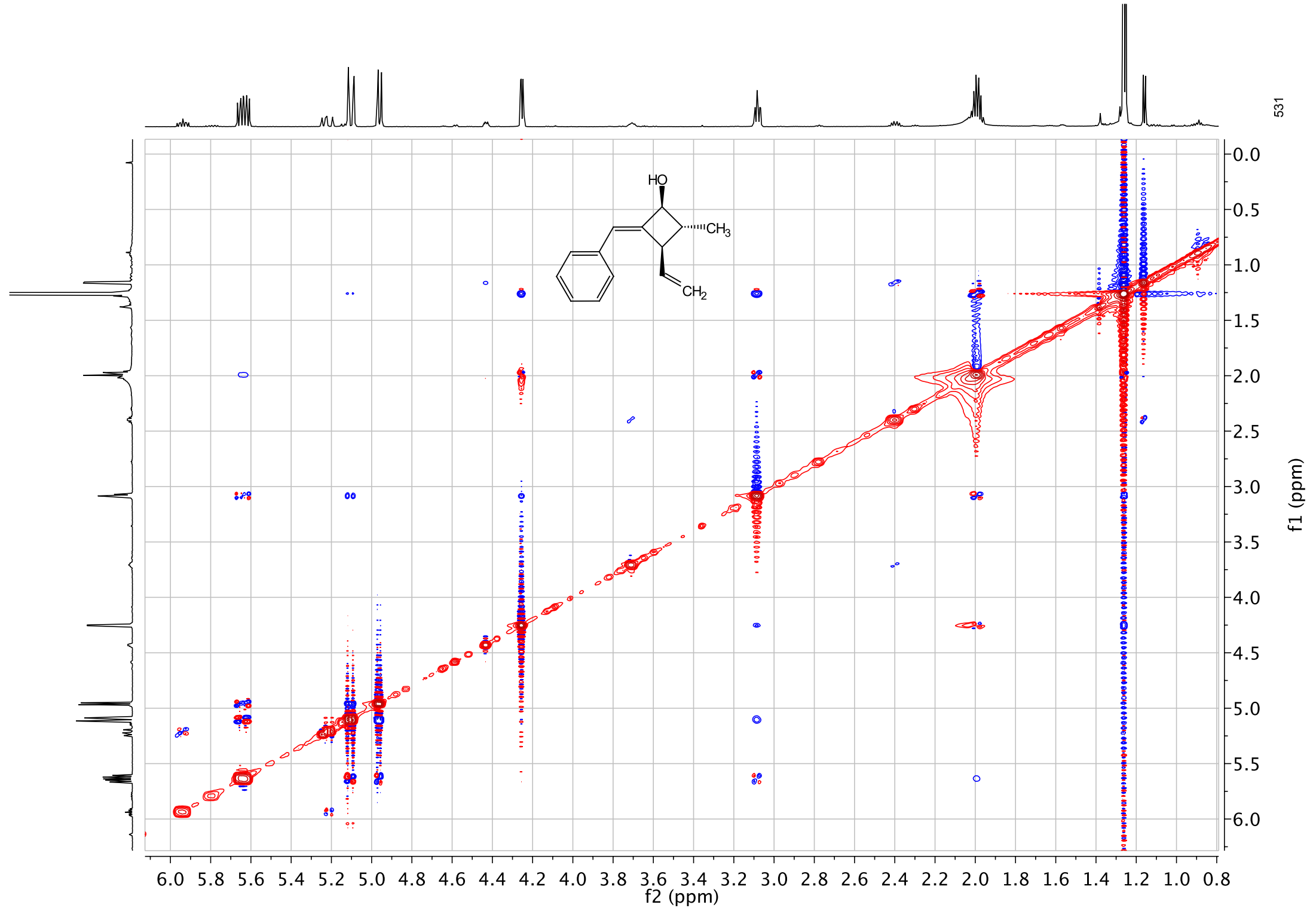


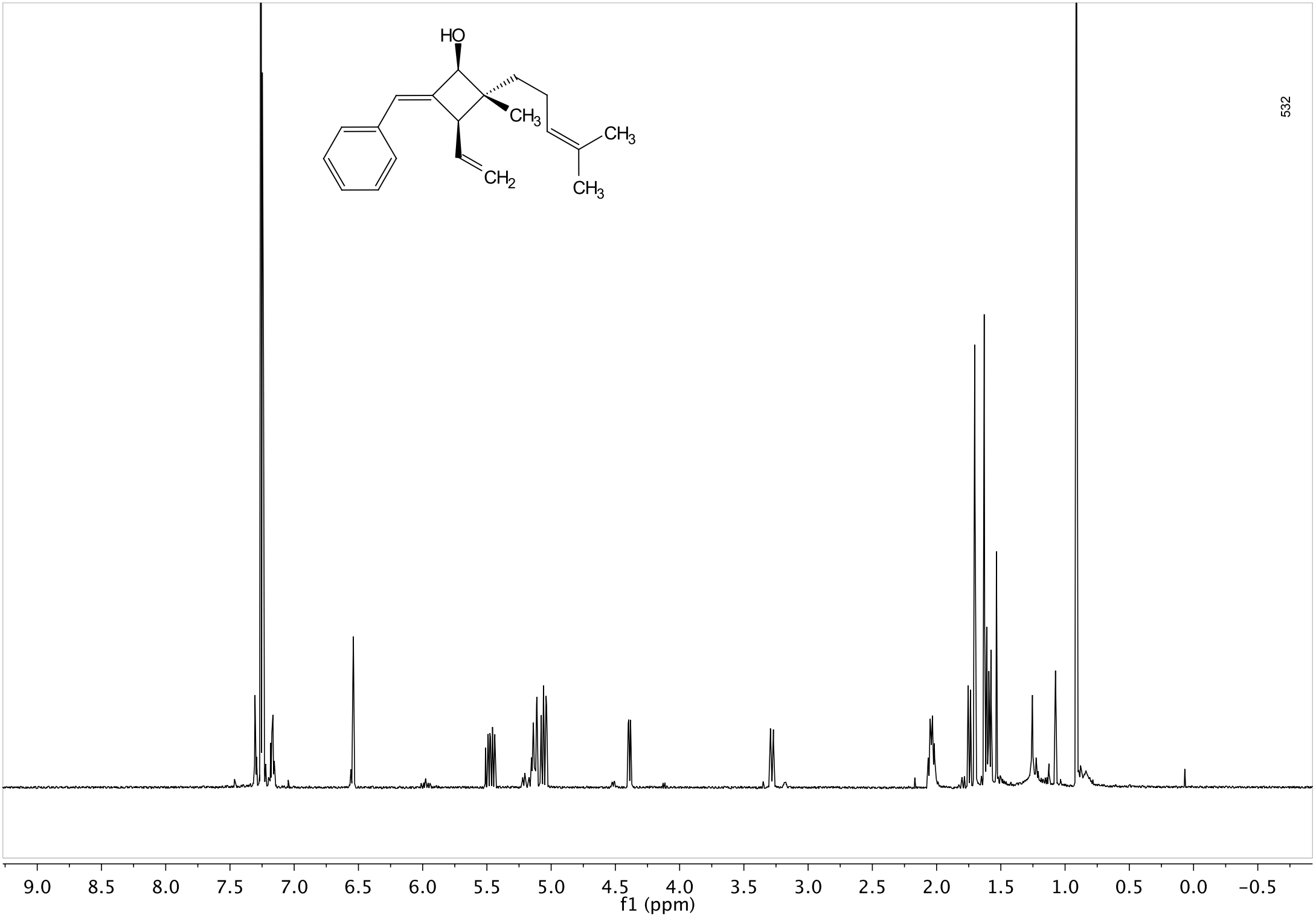

529

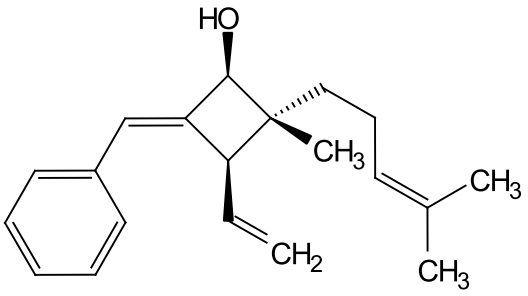
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

f1 (ppm)


HO
CH3
530
CH2
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)


HO
CH3
CH2
531
f2 (ppm)
f1 (ppm)
6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0

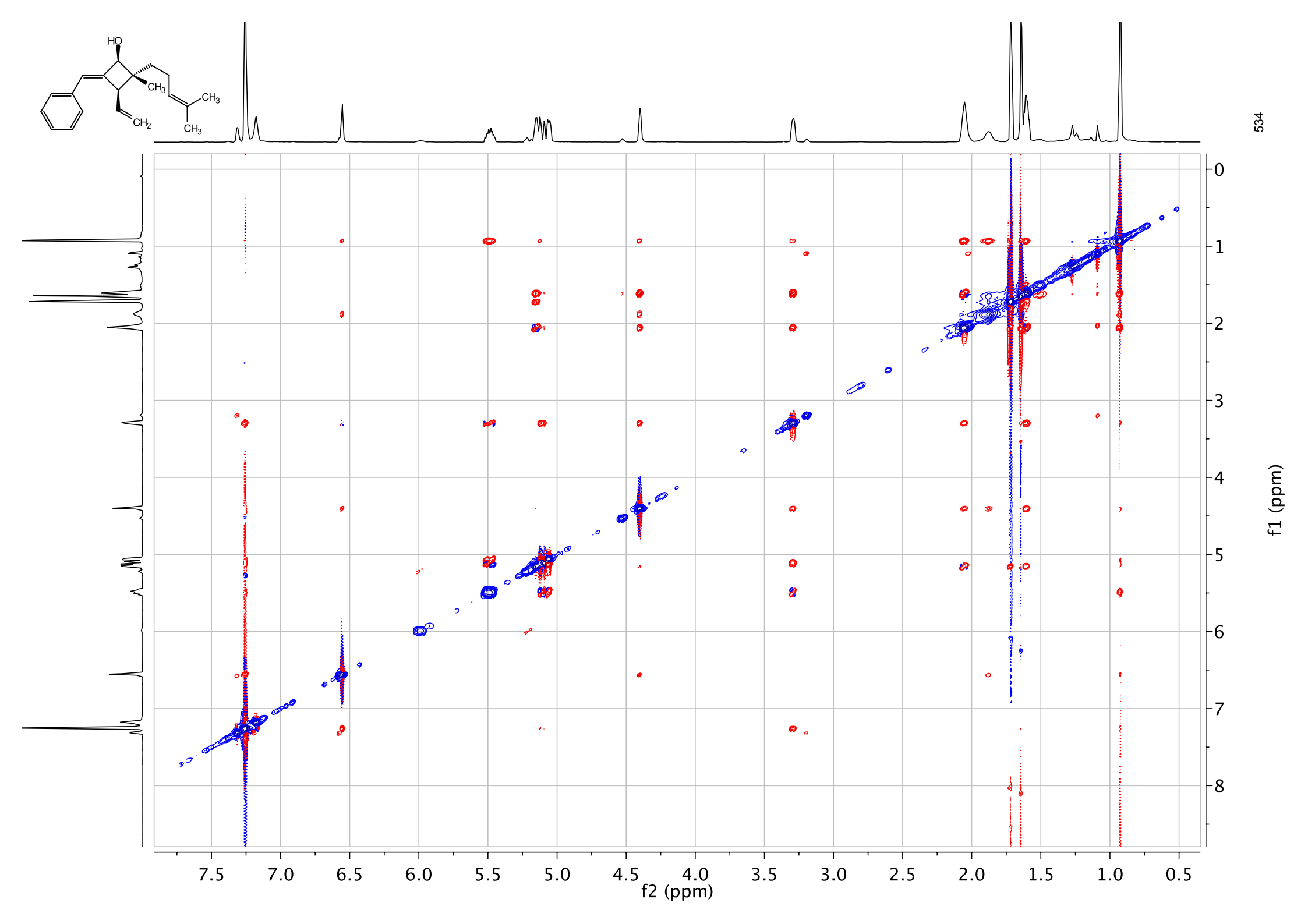

HO
CH3
CH3
CH3
CH2
532
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

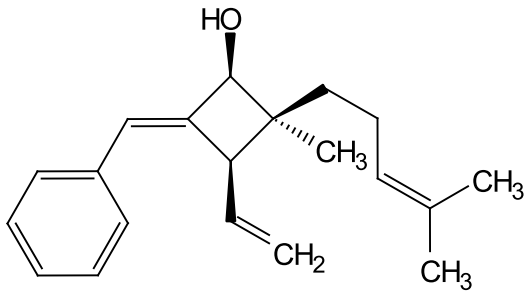



533

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

f1 (ppm)

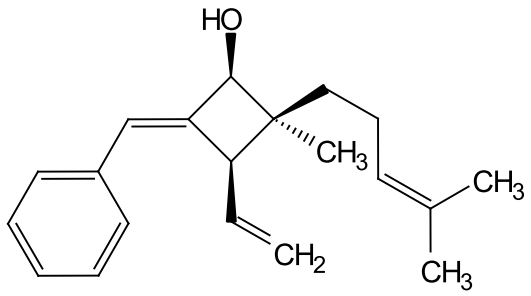

HO
CH3
CH3
CH2
CH3
534
f1 (ppm)
f2 (ppm)
0
1
2
3
4
5
6
7
8
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5




535

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

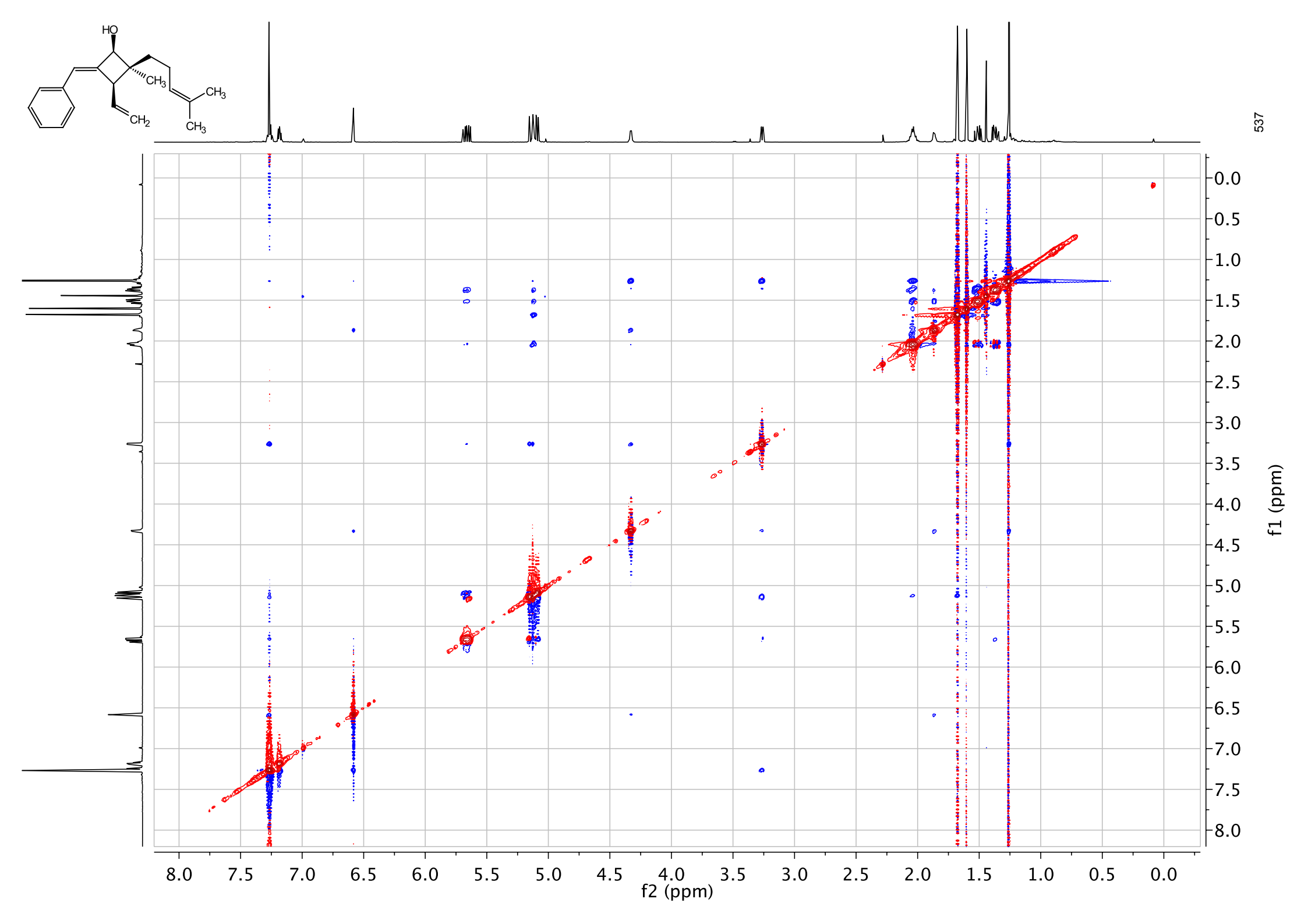
f1 (ppm)

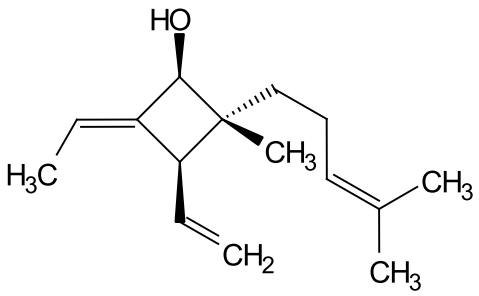



536

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

f1 (ppm)

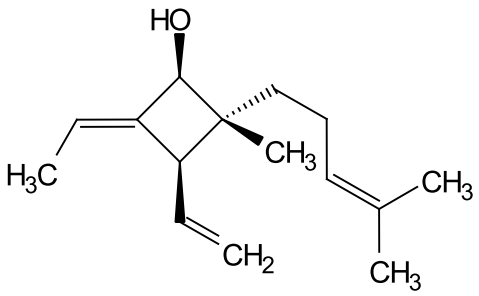

HO
CH3
CH3
CH3
CH2
537
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0




538

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1

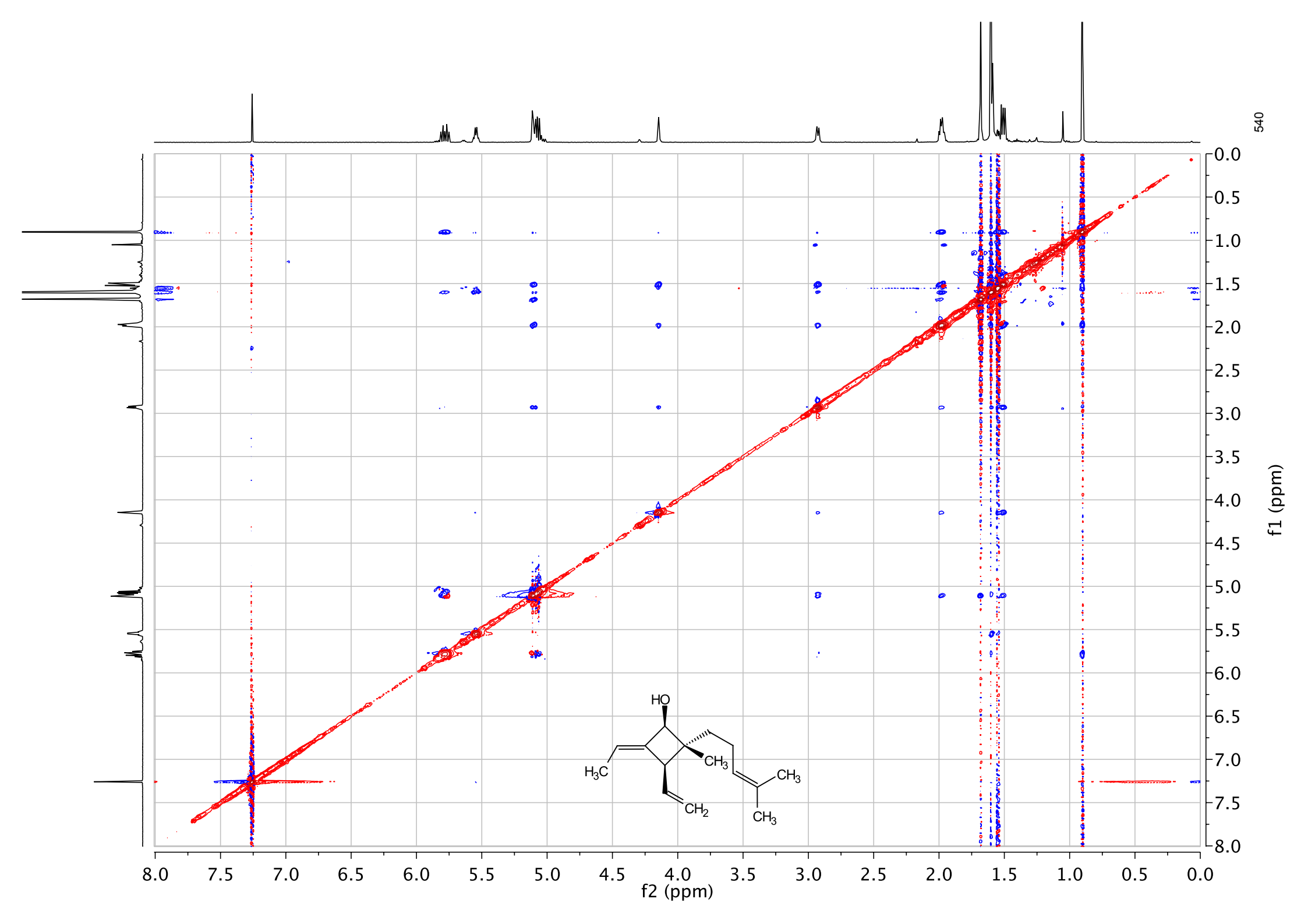
f1 (ppm)



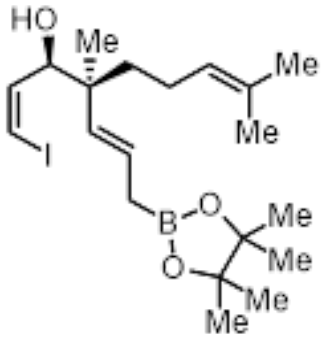

539

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

f1 (ppm)


540
f1 (ppm)
f2 (ppm)
HO
H3C
CH3
CH3
CH3
CH2

400 MHz

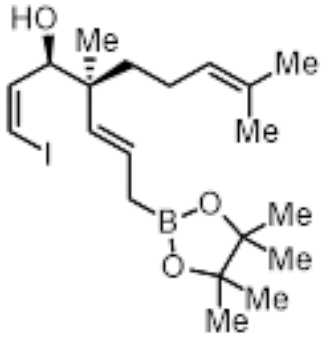



541

10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 -1.0

f1 (ppm)

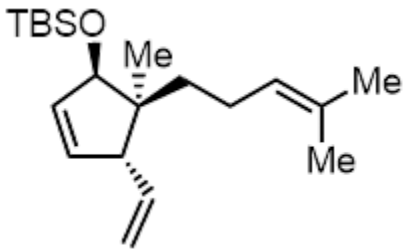
400 MHz




542

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

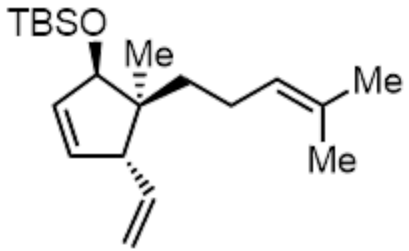
f1 (ppm)




543

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1.0 −1

f1 (ppm)

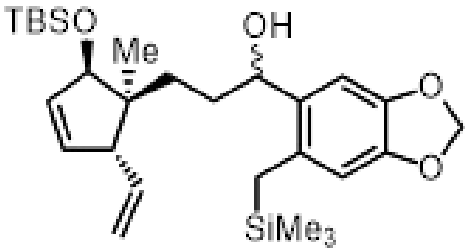



544

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

f1 (ppm)

400 MHz

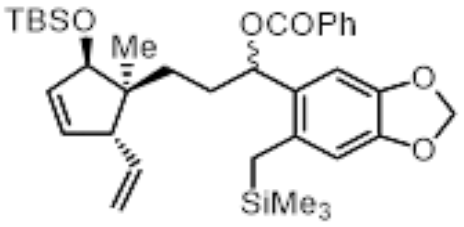



545

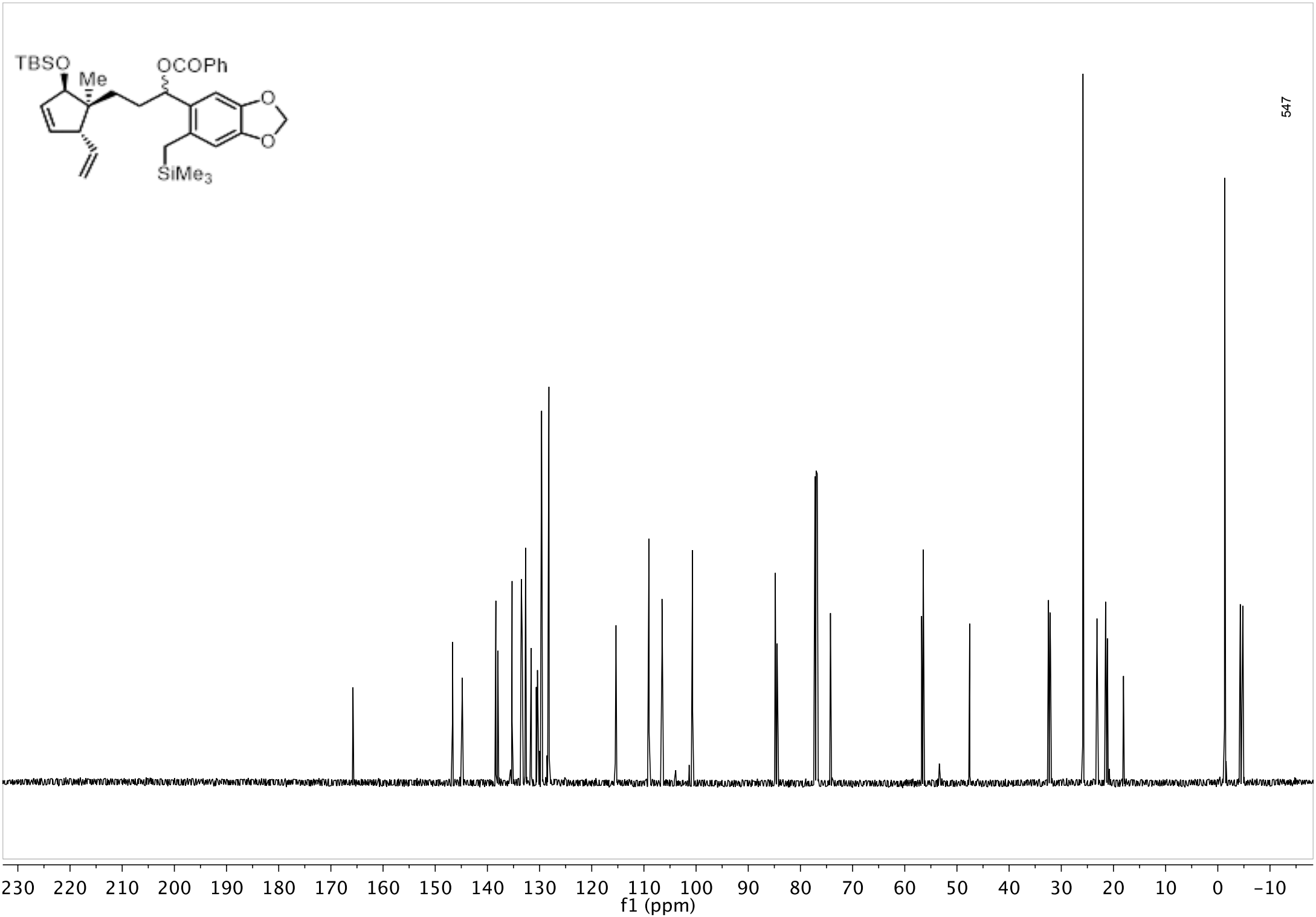
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 -1.0

f1 (ppm)

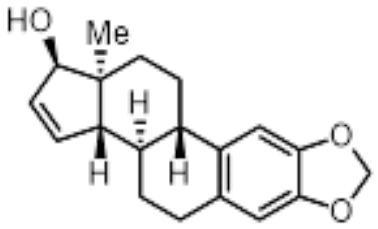
400 MHz




546


TBSO
Me
OCOPh
O
O
SiMe3
547
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

400 MHz

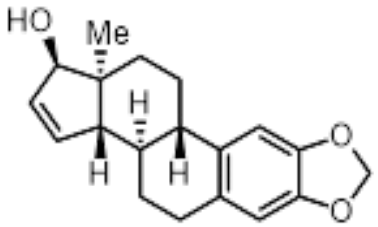



548

10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 -1.0

f1 (ppm)

400 MHz




549

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)